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# Abstracts: XXII Bárány Society Meeting

**B1.1**
**Impulse testing and irregular afferents**
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Over the last 30 years, we have learned a great deal about the physiology of the vestibular organs in mammals. Over roughly the same period, there has been a parallel effort in humans, in part to develop diagnostic tests for peripheral disorders and in part to study the peripheral origins of human spatial orientation. The interaction between human and animal studies is not unidirectional: in many cases, human studies have clarified issues of basic interest. As an example of this two-way interaction, we can consider impulsive testing, which has proved a sensitive indicator of canal function. It is usually assumed that response asymmetries are the result of silencing of afferents during brief, inhibitory rotations. The evidence for and against this proposition will be considered. One interpretation is that irregularly discharging afferents, which are the most easily silenced fibers, may contribute to the initial phase of the AVOR. It can even be argued that these are the only afferents that can be recruited on a millisecond time scale. The distinctive contributions of the various afferents has remained a basic problem of some importance. In this case, clinical studies have contributed to a possible solution to the problem. One might even argue that the session should have been called "From Bedside to Bench" or, at the very least, "Between Bedside and Bench"

**B1.2**
**Impulsive testing of semicircular function: from bench to bedside, from bedside to bench**
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The idea that one could test semicircular canal function by observing the eye response to a single head turn probably started with Plum and Posner. In their papers on the diagnosis of stupor and coma they made much of how useful it was to observe the "doll's head reflex" as they called it, in order to assess the integrity of the brainstem pathways between the vestibular and the ocular motor nuclei, the integrity of the peripheral vestibular system being assumed. The idea that one could test peripheral semicircular canal function, one side at a time, by observing the eye response to a single high-acceleration head turn was based on knowledge of Ewald's second law; that ampullopetal displacement on the lateral semicircular canal produces a larger nystagmus response that ampullufugal displacement. To make a head impulse test one also needs to know that the latency of the vestibulo-ocular reflex is much shorter than that of smooth pursuit and of saccades and that the peak velocity of the vestibulo-ocular reflex is much higher than that of smooth pursuit or the cervico-ocular reflex. If one now adds knowledge of the semicircular canal planes and of 3-dimensional rotations one can measure the function of any single canal individually. Observing the tell-tale sign of impaired semicircular canal function, the compensatory saccade during a rapid head rotation only requires clinical practice. Understanding what is behind it requires scientific knowledge. The head impulse test has now returned from the bedside back to the bench. Recordings of primary afferents are showing why acceleration is indeed the key to the head impulse test; that via regular and irregular afferents the semicircular canals sense both velocity and acceleration. The vital partnership between bench and bedside, bedside and bench continues.

**B1.3**
**Complementary Interactions Between Basic and Clinical Research in the Vestibular System**
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The close relationship between the vestibular end organs and the reflexes they control provides a useful basis for understanding the pathophysiology of many vestibular disorders. Also, studies that are motivated by a desire to understand the symptoms and signs of vestibular dysfunction have provided new insight into basic vestibular mechanisms. Examples of each approach will be discussed.

Superior canal dehiscence syndrome is an inner ear disorder caused by an opening in the bone overlying the superior semicircular canal. Patients with this disorder can experience vertigo and oscillopsia in response to loud sounds or to maneuvers that change middle ear or intracranial pressure. The opening in the bone overlying the superior canal creates a third mobile window to the labyrinth. Recognition that the evoked eye movements align with the plane of the affected superior canal was the crucial step that led to the identification of the syndrome.

Disorders of gaze control created by vestibular dysfunction are most pronounced for high-frequency, high-acceleration head movements. Until recently, most investigations in basic vestibular physiology have been performed using motion stimuli that are of lower frequency and acceleration when compared to the natural range of head movements in primates. Studies of the vestibuloocular reflex and of the responses of vestibular-nerve afferents to higher frequency and acceleration head movements have revealed mechanisms of signal processing had not been elucidated previously.

**B2.1**
**Audio-Vestibular Findings in Patients with Superior Canal Dehiscence Syndrome**
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Recently Minor and co-workers described patients with sound and pressure induced vertigo due to dehiscence of bone overlying the superior semicircular canal. Since then 13 patients with the superior canal dehiscence syndrome have been diagnosed at our clinic. The patients had had symptoms for varying periods of time but none of them had had symptoms since childhood/adolescence. There was no obvious explanation why symptoms started, i. e. the onset was not systematically related to head trauma, barotrauma etc. There was, however, a familial appearance of the disorder, i. e. two of the present patients were brothers.

All 13 patients reported pressure-induced vertigo that increased during periods of upper respiratory infections. Gaze instability during head-movements was also a common complain. A vertical/torsional eye movement related to the superior semicircular canal was seen in most patients at pressure changes and/or at sound stimulation. One patient did also have paroxysmal nystagmus/vertigo at sitting up related to the superior canal dehiscence.

The patients also had hyperacusis to bone-conducted sounds. All 13 lateralized Weber's test to the symptomatic ear. Some of the patients also reported pulse-synchronous tinnitus. A few also had more severe hypersensitivity for "internal sounds" and could hear their eyes move, hear movements of the intestines during walking etc. The audiogram did, in some of the patients, reveal a small conductive hearing loss in the low frequency range. The hearing loss was not a sign of a conductive disorder in the middle ear, because the patients all had normal stapedius reflexes. Instead the low frequency air-bone gap could, theoretically, be explained by a combination of the conductive hyperacusis and an "intralabyrinthine conductive hearing loss", i. e. loss of acoustic energy in response to stapes movements due to the (abnormal) volume displacement within the vestibular apparatus and/or due to changes in the inner ear impedance.

Testing vestibular evoked myogenic potentials revealed in all but one patient a vestibular hypersensitivity to sounds. In response to clicks and to tone-bursts in the low frequency range the VEMP were very large with a low threshold.

The coronal high-resolution CT-scans showed the skull base to be rather thin and cortical bone separating the middle ear and the antrum from the middle cranial fossa was absent bilaterally in many of the patients. The dehiscence of the superior canal was visible in all symptomatic ears. Also in some non-symptomatic ear the CT-scans suggested a dehiscence. Hence, it is important not to rely exclusively on CT-findings for the diagnosis of a superior canal dehiscence syndrome but also to test for vestibular hypersensitivity to sounds and pressure changes.

Two of the patients have undergone plugging of the superior semicircular canal using a transmastoid approach and both patients were relieved of the pressure-induced symptoms. A third patient is scheduled for surgery. A fourth patient has incapacitating symptoms but surgery is not considered an option because of deafness on the other ear.

**B2.2**

**Superior Canal Dehiscence: Etiology, Imaging, and Mechanisms of Pressure- and Sound-Induced Vertigo**

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Evidence suggests that a developmental abnormality underlies superior canal dehiscence syndrome (SCDS). We examined 1000 adult temporal bones sectioned through the superior canal (SC) and found 5 dehiscences and 14 "near" dehiscences (<0. 1 mm of bone). Half of affected individuals had thinning or dehiscence bilaterally. No erosive lesions were found at the dehiscences. We also examined 27 pairs of temporal bones from infants and children <4 years old and found that the thickness of bone over the SC at birth was typically < 0. 1mm, and that bone growth continued here for 3 years before adult thickness was reached. We suggest that arrest of this development may predispose some individuals to a dehiscence.

Further evidence in support of a developmental etiology comes from a review of CT scans from 27 patients with SCDS (20 unilateral, 7 bilateral) and 88 controls with other otologic disorders. CT scans obtained with 0. 5 mm collimation were reconstructed in the plane of the SC. Bone overlying the SC in controls was 0. 67±0. 38 mm thick (mean ± SD). Thinner bone was found over the SC on the intact side in patients with unilateral dehiscence (0. 31±0. 23 mm, p<0. 0001). These findings suggest that SCDS arises in patients with abnormally thin bone over both SCs. A second event, such as trauma or erosion from pulsation of the dura and brain, may disrupt this thin bone.

Conventional axial and coronal temporal bone CT scans with 1. 0 mm collimation have good sensitivity but relatively low specificity for the identification of SC dehiscence. Partial volume averaging can result in apparent dehiscence when a thin layer of bone is present. With 0. 5 mm collimation and multiplanar reconstruction of the data, bone as thin as 0. 1 mm should be detectable. However, the diagnosis should not be made on CT findings alone, but in conjunction with confirmatory clinical evidence.

The mechanisms of pressure- and sound-induced vestibular stimulation after SC fenestration were examined in anesthetized chinchillas with extracellular recordings from the superior vestibular nerve. Fenestration of the SC rendered all SC afferents sensitive to pressure applied to the external auditory canal, but fewer than half of afferents from other endorgans responded, and their responses were smaller. The direction of the SC afferent responses agreed with predicted endolymph flow within the SC. Rigidly sealing the fenestra abolished pressure responses but maintained rotational sensitivity. While canal and otolith afferents in the intact labyrinth did respond to sufficiently loud (117-135 dB SPL) acoustic stimuli, fenestration of the SC lowered the acoustic thresholds (77-124 dB SPL). Two types of acoustic responses were noted. Tonic responses, seen only in regularly discharging afferents, consisted of slow changes in firing rate to new levels, followed by adaptation. These responses resembled the afferents' responses to steps of head acceleration. Phasic responses, seen mostly in irregularly discharging afferents, consisted of phase-locked responses to the acoustic fundamental frequency or its integral divisors, suggesting that the vestibular hair cells are capable of following very high-frequency stimuli.

**B2.3**

**Superior Canal Dehiscence Syndrome: Clinical Manifestations, Pathophysiology, and Treatment**

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We have described a syndrome of vertigo and oscillopsia evoked by loud noises and/or by pressure stimuli in patients with dehiscence of bone overlying the superior semicircular canal. The dehiscence creates a « third mobile window » into the inner ear and renders the superior canal responsive to sound as well as to maneuvers that change middle ear or intracranial pressure. We have diagnosed this syndrome in 41 patients (25 men, 16 women) over the period from May 1995 through April 2002. The median age at the time of diagnosis was 43 years (range: 20 - 70 years). The symptoms and signs were unilateral in 33 patients and bilateral in 8 patients.

The evoked eye movements in this syndrome typically align with the plane of the dehiscent superior canal when the dehiscence measures < 5 mm in length. Loud tones, positive pressure in the external auditory canal, and Valsalva against pinched nostrils can lead to a nystagmus that corresponds to ampullofugal flow and excitation of the affected superior canal. Negative pressure in the external auditory canal, Valsalva against a closed glottis, and jugular venous compression can lead to a nystagmus that is indicative of ampullopetal flow and inhibition of the dehiscent superior canal.

Patients with superior canal dehiscence syndrome who do not have a history of prior middle ear disease or prior middle ear surgery have a diminished threshold (typically < 85 dB) and increased amplitude for vestibular-evoked myogenic potentials on the side of the dehiscence.

The auditory symptoms associated with superior canal dehiscence include hypersensitivity to bone-conducted sound, pulsatile tinnitus, and an audible sensation of eye motion. We have identified 5 patients with an air-bone gap on audiometry of sufficient magnitude to raise a suspicion of a middle ear cause of conductive hearing loss. Yet, each patient had intact VEMP responses and acoustic reflexes, findings that would not be expected if the air-bone gap were due an ossicular abnormality. Three of these patients did not have sound- or pressure-induced vestibular symptoms. Stapedectomy had been performed in 3 patients prior to the diagnosis of superior canal dehiscence, and in no case was the air-bone gap reduced post-operatively. High-resolution temporal bone CT scans confirmed the presence of superior canal dehiscence in each case.

Surgical correction of the dehiscence through a middle cranial fossa approach was performed in 11 patients in whom the vestibular symptoms were debilitating. Canal plugging was used in 4 patients and resurfacing of the canal with fascia and bone in 7. Complete relief of symptoms was achieved in 9 patients and partial relief of symptoms in 2 patients. Transient sensorineural hearing loss occurred in 2 patients after revision procedures.

**B3.1**

**Do the same rules govern arm trajectory formation and the steering of locomotion?**

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Several simplifying rules govern arm trajectory formation. For example the relation between curvature and tangential velocity, antiphase relations linking the segments of the arm and forearm, Listing's law, the separate coding of distance and direction etc…

We have put forward the hypothesis that similar rules also govern the formation of locomotor trajectories. In previous work we have shown that the head is stabilized in space in rotation providing a stable inertial guidance platform (Pozzo et al. , 1990), and that there is a separate coding of distance and direction and we have suggested that the vestibular system contributes to the coding of direction, probably through the head direction cell system which has a separate neural mechanisms from the neural system coding rotations and translations. (Berthoz et al. , 1999) Recently, we have also shown that the 2/3rd power law applies to the generation of elliptical locomotor trajectories (Vieilledent et al. ,2001). Here (Glasauer et al., 1993;Glasauer et al. , 2002;Grasso et al. , 1996;Grasso et al. , 1998b;Grasso et al. , 1998a; Grasso et al., 1998c;Takei et al., 1997) we shall provide evidence that these properties (Pozzo et al., 1991)are also valid for complex locomotor trajectories.

We have measured head and trunk movements during locomotion along complex paths with in a large hall with a 24 camera system ( Vicon) ( ATOPOS company). Specifically, the paths examined were figures-of-eight, folded ellipses and the cloverleaf. In all cases a robust inverse variation of velocity with path curvature was seen. As in the case of the 2/3rd power law seen in the elliptical trajectories, the measured variations were shown to be between the instantaneous velocity and curvature. However, paradoxically, the form of this local law appears to be shape dependent, suggesting an interaction between local and global planning of the locomotor trajectory.

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**B3.2**

**The Broken Escalator Phenomenon: After Effect of a Gait Adaptation**

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People commonly report that when they walk onto an escalator which is broken, and therefore stationary, they experience an odd sensation and their balance seems momentarily disturbed. We examined the physiological basis of these subjective reports and found that, when walking onto a stationary surface which was previously experienced as moving, people walk too fast (0. 70m/s compared with 0. 61m/s baseline; p<0. 01) and sway excessively (peak forward sway=11. 3cm, compared with 3. 4cm baseline; p<0. 01), despite full awareness that the surface will remain stationary. The broken escalator phenomenon therefore reflects the inappropriate expression of a learned locomotor behaviour. This aftereffect demonstrates dissociation between the declarative and procedural systems of the central nervous system (CNS). The findings suggest that locomotor adaptation is less susceptible to cognitive influence than other types of motor learning.

**B3.3**

**Posture and gaze during circular locomotion**

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Continuous circular locomotion presents a significantly great challenge to the vestibulo-collic and vestibulo-ocular reflexes. The vestibular system must react to the continued centripetal acceleration, which not only is a continuous lateral linear acceleration, but gives a sustained GIA tilt relative to the direction of gravity. How the vestibular system codes the compensation and orientation of the head to this gravito-inertial stimulus is not known. For example, it is not clear how continuous circular locomotion impacts on the stride length re frequency of stepping at different velocities of walking. It is also not known how the head fixation point is affected by the circular walking. More importantly, it is not clear how the angular and linear vestibulo-ocular reflexes respond to continuous circular locomotion, which invokes velocity storage.

The purpose of this study was to characterize the strategies of gait adapted for circular locomotion and determine how the compensatory and orienting functions of the lVOR help maintain stable gaze under a continuous altered GIA from when the subject is standing upright or walking straight. Head, eye, and body movements of 4 subjects were measured during circular locomotion while walking around the perimeter of a 1. 2-m radius disc. Subjects walked at slow, moderate or fast (90 deg/s) velocities for 60 sec in light. And they walked in dark while holding onto a bar, which circled with them at moderate velocities for 60 sec. And in order to compare, the subjects walked on linear treadmill at the 0. 4, 0. 6, 0. 8, 1. 0, 1. 2 and 1. 4 m/s walking speed. Head and body position in space were measured with a motion analysis system. 3D eye movements were recorded with a video-based eye movement monitor (Imai et al, 1999). they walked in dark while holding onto a bar, which circled with them.

The conclusion was the following.

1. In order to increase walking velocity, during straight walking, stride length is more important than step frequency. But, during circular locomotion, step frequency is more important than stride length.

2. During circular locomotion, orienting response works, so head roll angle re trajectory increase as GIA roll angle increase. The gain is about 0. 8. But for trunk, orienting response doesn't work, so trunk is always upright regardless of GIA roll angle. Eye roll is compensate the roll of the head. So angular VOR works during circular locomotion.

**B3.4**

**Evaluation of Human Locomotion by Trajectories of the Center of Force in Patients with Vertigo**

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Vestibular system disorders can cause abnormal locomotion, and the pattern of abnormality might reflect the site of lesion. With this in mind, an analysis of human locomotion was performed by attaching a tactile sensor onto each foot in patients with vestibular system disorders. Fifteen cases with vestibular neuronitis and tweleve cases with spinocerebellar degeneration comprised the patient group. The average age of the vestibular group was 55.5 and that of the spinocerebellar group was 52.3. Fifteen healthy adults served as controls. Subjects were asked to walk staight over a distance of nearly eight meters (free gait) with eyes open or closed. For the present study, we have focused on the following two points: progression of the center of force and values obtained by calculation of average length of trajectories of the center of force divided by step length. Regarding foot pressure progression, three parts were determined during stance and checked for regularity. These parts were period of body weight acceptance, body weight translation and body weight thrust. We also checked for pressure differences between both feet. In cases with vestibular neuronitis, foot pressure progression was mostly stable despite the lesion when measured with the patients' eyes open. Foot pressure progression became somewhat irregular during weight acceptance and the period of weight translation with the eyes closed. On the other hand, in cases with spinocerebellar degeneration, instabilities became greater during stance in general, especially in weight acceptance and the period of translation. Pressure differences became greater in the foot on the lesion side than on the intact side, indicating a shift of the center of gravity to the lesion side during locomotion. The average length of trajectories of the center of force became longer in the spinocerebellar group, and even shorter in the vestibular neuronitis group. These changes reflect the underlying disorder in the vestibular system, which was manifested as a vestibulo-spinal abnormality. The physiological and clinical significance of these findings will be discussed.

**B3.5**

**Both actual and imagined locomotion suppress spontaneous vestibular nystagmus**

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Vestibulo-ocular and vestibulo-spinal motor responses use common vestibular input and partially overlapping neuronal networks. It is not known if and to what extent these responses are linked functionally or if they operate separately.

Therefore, slow-phase velocity (SPV) of spontaneous nystagmus was measured during standing and walking in patients with acute unilateral vestibulopathy due to vestibular neuritis (n=6). To avoid interference between the physiological vestibulo-ocular reflex and the spontaneous nystagmus, the differential effects of imagined standing, walking, and running on spontaneous vestibular nystagmus were also evaluated (n=10; mean age 49 years, range 30-74 years, 2 females).

We found that in patients with acute vestibulopathy due to vestibular neuritis spontaneous vestibular nystagmus was suppressed both during actual and imagined locomotion. Recordings by video-oculography in six patients showed that the mean peak SPV of the horizontal nystagmus was 14. 0±5. 8 deg/s while standing upright in

complete darkness; this decreased by 26% to 10. 5±4. 8 deg/s during locomotion (ANOVA, F(1,5)=10. 2; p=0. 02).

Mean peak SPV of the horizontal nystagmus was 11. 1±5. 8 deg/s during actual standing and 10. 8±5. 8 deg/s during imagined standing at a bus stop. During the imagination of slowly walking down a country lane, SPV decreased by 26% to 8. 2±4. 7 deg/s and by 42% to 6. 3±2. 8 deg/s during the imagination of running down a grassy hill (Bonferroni: standing vs. imagination of running p<0. 003).

A functional link was demonstrated between vestibulo-ocular and vestibulo-spinal mechanisms. Patients suffering from vestibular neuritis benefit from the suppression of spontaneous nystagmus for it alleviates the disturbing impression of movement of the visual scene (oscillopsia) caused by involuntary eye movements.

**B3.6**

**Multimodal signal integration in the primate fastigial nucleus**

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The rostral part of the primate fastigial nucleus (rFN) is presumably involved in vestibulospinal mechanisms. It received Purkinje cell (PC) input from the overlying anterior part of the cerebellar vermis, is reciprocally connected to the vestibular nuclei, and also sends some direct projections to the spinal cord. Recent single unit recordings in our laboratory revealed complex response characteristics in most vestibular neurons in the rFN: in many cells, converging inputs from semicircular canal (SCC) and otolith signals could be identified, and practically all neurons exhibited evidence of "spatio-temporal convergence" (STC). We were able to show that the vast majority of responses could be mathematically described as the simple linear sum of - spatially and temporally diverse - cosine tuned input signals ("linear STC"). However, the frequency-dependent changes in the spatio-temporal properties of some neurons, which showed large drafts of their preferred orientation (PO) and/or response phases across frequencies, could not always be reduced to simple linear interaction of signals from primary vestibular afferents.

To study if, and how, manipulating body-re-head-position influences vestibular signals and frequency-dependent properties of rFN neurons in the alert primate, we recorded from single rFN neurons in the monkey during sinusoidal vertical vestibular stimulation (0. 1-1. 0 Hz) at different trunk positions (45° left, center, 45° right re head). At each trunk position, units were tested at 2 orthogonal stimulus orientations (roll and pitch). Taking advantage of the linear-STC-property of rFN units (see above), this approach allows to calculate the response parameters for all intermediate vertical stimulus orientations. The vestibular responses of most units investigated so far clearly depended on trunk-re-head-position. In most cases, shifts of the PO were observed which (partly) compensated for the positional manipulations, so that the neuronal PO was, on average, more closely related to trunk- than to labyrinth orientation. Moreover, controlling trunk orientation reduced the occurrence of large phase and PO drifts in the neuronal sample.

These results indicate that the rFN integrates proprioceptive signals from neck receptors to contribute to a fundamental function in vestibulospinal reflex generation, namely the appropriate redistribution of reflex activity during positional changes of effector vs. sensory organs. Controlling proprioceptive inputs is clearly required for any movement and may simplify attempts to understand or model the multimodally shaped vestibular signals in the rFN.

**B3.7**

**Does Vestibular Stimulation Contribute to the Lack of Perception of Podokinetic After-Rotation?**

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After prolonged stepping-in-place relative to space on the centre of a rotating turntable, blindfolded subjects are unable to step in place on a stationary surface. Instead they unconsciously step themselves around in a direction opposite to that of the previously rotating turntable, a phenomenon termed podokinetic after-rotation (PKAR). Why should this rotation not be sensed when PKAR angular velocities extend well above the threshold of vestibular sensation?

We set out to test the hypothesis that minimal vestibular feedback may control the rate of rise of PKAR velocity in such a way as to constrain the afferent vestibular signal close to its sensory threshold throughout the initial phase of PKAR acceleration. We devised a method for recording PKAR-driven foot rotation relative to the trunk while servo-stabilizing the trunk relative to space. Trunk rotation was sensed by an electromagnetic search coil whose reversed output was fed into the velocity-controlled servo-motor driving the turntable. Thus the subject's angular position relative to space caused the turntable to rotate in an opposite direction at a speed proportional to the instantaneous angular position of the subject relative to the starting position. As a result, with suitable feedback gain the subject remained approximately stationary in space during PKAR and the turntable tachometer registered PKAR velocity of foot rotation re trunk in the absence of significant vestibular stimulation.

Preliminary results indicate that the rate of rise of PKAR velocity during trunk stabilization was around four times higher than that during normal PKAR, arguing in favor of the above hypothesis.

**B3.8**

**Orienting Linear Vestibulo-Ocular And Vestibulo-Collic Refexes During Turning And Centrifugation**

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When turning a corner there is a low-frequency linear acceleration experienced due to the centripetal acceleration directed towards the center of the turn. This sums with gravity to tilt the gravito-inertial acceleration (GIA) vector in the subject's roll plane into the turn, inducing corresponding head tilts. For example, when walking around a 90 deg turn with a radius of 0. 5 m at a moderate adult walking speed (1. 5 m/s) the head experiences a

centripetal acceleration of up to 0. 4-g that tilts the GIA 21 deg with respect to the subject's head. Subjects tilt their heads into the turn, minimizing the tilt of the GIA relative to the head, with a gain of around 38% of the peak GIA magnitude. The onset of the head roll tilt tends to anticipate the onset of the GIA by approximately 200-400 ms, with peak head roll of approximately 8 deg occurring just prior to the peak in the GIA. This orienting low-frequency linear vestibulo-collic reflex (lVCR) aids in the maintenance of balance when turning corners. The eyes also roll relative to the head in the same direction as the head roll with a magnitude of 1-1. 5 deg. Thus, an orienting linear vestibulo-ocular reflex (lVOR) tends to align the eyes with the tilted GIA vector. The duration of the ocular torsion closely approximates the duration of the tilt of the GIA, and there is no anticipation of roll eye orientation. At the end of the turn the head slowly rolls back to the upright position and the eyes reorient to 0 deg following the GIA.

Preliminary data from subjects undergoing centrifugation with the head free demonstrate a similar orienting lVCR in response to sustained interaural linear acceleration. Subjects roll-tilt their head towards alignment with the GIA with a gain of approximately 40% for interaural accelerations of up to 0. 3-g. For centripetal accelerations above this magnitude the lVCR response is overwhelmed and the head tilts way from the axis of rotation. There is a delay in the response at the onset of centrifugation that is likely due to the dynamic properties of the head movement control system.

The anticipatory head roll observed when walking around corners may be due to an adaptation of the head movement control mechanism to help overcome its inherent dynamic properties. This would aid in the alignment of the head to the GIA during sharp turns. Supported by DC03284, NCC 9-58 (NSBRI), NY State HEAT grant, EY01867, NCC 9-128 and DC05222.

**B3.9**

**Anticipatory and reactive control of bipedal walking in the Japanese monkey, M. fuscata**

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We have shown previously that the young Japanese monkey, whose natural terrestrial locomotion is quadrupedal (Qp), can be operantly-trained to walk bipedally on the moving treadmill belt [1,2]. Such trained animals can clear an obstacle attached to the surface of the treadmill belt. If they stumble and collide with the obstacle, they quickly compensate for the perturbed posture, and resume bipedal (Bp) walking [3,4]. These findings suggested that the monkey use both anticipatory and reactive control mechanisms while elaborating Bp locomotion. To explore the relative contribution of anticipatory and reactive mechanisms, we have now examined precisely how the Bp walking monkey clears an obstacle on the walking path. During a stumble, we have also examined the kinematics of multiple motor segments (head, neck, trunk, upper and lower limbs).

An adjustable-height rectangular block (width, 25 cm; length, 5 cm; height, 2. 4, 5. 9 or 7. 0 cm) was placed on the left side of a treadmill belt. Belt speed was set at 0. 7, 1. 0, or 1. 3 m/s. A single block obstacle was arranged to confront the left hindlimb every 4-6 steps, depending on belt speed [4]. During initial trials, the monkey often stumbled. This involved the left toe either slipping up the block's initially encountered vertical surface or making contact with the obstacle's top surface. After several sequential trials on the first day of encounter with the obstacle, the number of stumbles in a single training trial was reduced: i. e., the monkey quickly learned how to clear the obstacle, by use of what in humans has been termed a "hip-knee flexion strategy". When the obstacle's height was raised, there was a corresponding increase in hip/knee joint flexion of the left hindlimb so as to produce sufficient clearance space above the obstacle. Even when the in-coming obstacle was still out-of-sight, the monkey walked with this anticipatory strategy. When the monkey failed to clear the obstacle, it adopted a "defensive posture" to prevent falling. This was quickly followed by a "reactive compensatory posture," which enabled the animal to smoothly resume Bp walking.

During everyday human locomotion, the feet often collide with unexpected obstacles, thereby requiring compensatory postural and locomotor adjustments to prevent stumbling and falling, and reestablish normal walking. Previous human studies have shown that both reactive and anticipatory adjustments come into play when obstacles are encountered during walking. Yet to be determined is how such mechanisms are controlled within the central nervous system. This issue can now be addressed in our Bp-walking, Japanese monkey model.

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**B3.10**

**Pivot turns as whole-body gaze shifts**

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Patients with vestibular disorders frequently complain of unsteadiness or fall when turning. Concepts from current investigation of eye-head coordination have analogous considerations during turns. VOR gain modulation during gaze shifts, head-free pursuit and local feedback all have corresponding aspects during whole-body gaze shifts (pivot turns).

Methods. 20 subjects were studied over 24 experimental sessions, for 504 analyzed turns. Age ranged from 19-62 years. Instructions to standing subjects were simply: “turn to face the target” which was visible 75 or 90 deg horizontally. Pelvis and head yaw angular positions were recorded using a video motion detection system. The total duration of each turn (mean 1. 8 s) was divided into 100 intervals, which were assigned to one of three categories depending upon the relative velocity of the head and body over the interval. Intervals were labeled ‘*en bloc’* if head and body velocity were within 10 deg/s; ‘head on

body' if head velocity exceeded body velocity by > 10 deg/s; and 'stabilization' if head velocity was lower than pelvis velocity by 10 deg/s or more.

Results. Peak head velocity (max dH) was significantly greater than peak body velocity (max dP, see table). Significant head on body rotation during turns could be demonstrated in the position domain by calculation of maximum neck rotation, and in the velocity domain by comparing the pelvis and head velocity at a particular time (when peak head velocity occurred).

| Eyes opened 20 subjects | Max dH deg/s (range) | dP at max dH deg/s | Max dP deg/s | Max \|dN\| deg/s | max \|N\| deg |
|---|---|---|---|---|---|
| Right turns n = 246 | 123 ± 39 (57-233) | 69 ± 27 (10-144) | 85 ± 21 (44-154) | 63 ±30 (18-153) | 17 ± 9 (3-45) |
| Left turns n = 258 | 124 ± 42 (45-271) | 68 ± 27 (3-146) | 87 ± 21 (45-147) | 65 ± 32 (17-175) | 17 ± 10 (3-41) |

*En bloc* rotation of the head and body was present for ~40% of the duration of each turn, and occurred with greater likelihood at the beginning and end. Head on body rotation was present for ~23% of the time, most always during the initial portion of the turn. Stabilization of the head relative to the body occurred during the latter part of each pivot, accounting for ~34% of the total duration.

Conclusion. All pivot turns have intervals during which head and body in space velocity are significantly different due to head rotation on the body initially in the direction of the pivot turn, and later to stabilize the head in space whilst the body continues its turn. This is very reminiscent of head-free changes in gaze, except that during a pivot turn, head in space is the result of body in space and head on body rotation, making eye position (eye in head) comparable to neck rotation (head on body). During the initial portion of the turn, head and pelvis velocity are in the same direction, and head stabilization reflexes must operate at low gain. *En bloc* behavior is similar to head-free pursuit when head and target velocity are close. Stabilization of the head in space commences when the head reaches its desired position, and may involve the vestibulocollic reflex.

**B3.11**

**Normal and Vestibulopathic Recovery from Perturbations during Locomotion**

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Adapting to microgravity is not the only balance difficulty astronauts face. Major postflight problems include difficulties with standing, walking, turning corners, climbing stairs and other activities that require stability of upright posture and gaze. These difficulties inhibit the ability of astronauts ability to stand up, bail out, or escape from the vehicle during emergencies and to function effectively when leaving the space/shuttlecraft after flight. Any developed countermeasure must be tested to determine its effect on gait stability, particularly under those conditions that are most troublesome following spaceflight. These include, turning corners, climbing stairs, and recovering from perturbations during walking.

The aim of our first study was to develop a safe, standardized stability test and a set of metrics to characterize the recovery of gait stability in healthy individuals following a single mechanical perturbation during steady locomotion. Balance perturbations were mechanically applied to the right foot of 12 healthy subjects during paced walking by translating a platform embedded in a 12m walkway diagonally (+45/-135 degrees) relative to the direction of travel. We examined the medio-lateral (ML) displacement of the sternum before, during and after the perturbation. Measurements of ML position of the right and left shanks in relation to the position of the sternum were used as step-by-step estimates of the moment arm controlling ML motion of the body. We hypothesized that when gait is perturbed in the single stance phase of the step cycle, a series of steps after the perturbation will be altered reflecting an effort by the CNS to maintain the center of mass within the base of support and to stabilize the upper body for continued gait. Recovery of non-perturbation behavior was achieved on the third step after the perturbation.

The goal of the second study was to investigate the ML stability of gait in response of vestibulopathic subjects to surface perturbations. Nine subjects (mean age 52 years) with unilateral vestibular loss (100% Reduced Vestibular Response asymmetry from the caloric test) resulting from surgery for vestibular schwannoma were selected for this study. Despite their known vestibulopathy, all subjects scored within the normal range on computerized dynamic posturography (CDP) Sensory Organization Tests (mean score 72. 67).

We found that the VP population had greater changes in the ML moment arm in response to perturbations, as compared to the healthy population. In addition, the number of steps that it took for the oscillations of the ML moment arm to return within the normal range were greater for the VP population. In conclusion, analysis of dynamic ML stability during recovery from surface perturbations illustrates significant differences between healthy and VP subjects who had normal CDP responses. Thus, this approach may prove useful for characterizing subtle vestibulopathies and similar changes in the human orientation mechanism after exposure to microgravity

**B3.12**

**Kinematics Of Quadraupedal Locomotion After Semicircular Canal Plugging**

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A normal monkey and a monkey with all six semicircular canal plugged were trained to walk on a linear treadmill at various speeds, ranging from 0. 4 to 0. 9 m/s, which is the range of slow to fast walking in normal animals. The animals' body and head movements were recorded at 100 f/s using an OPTOTRAK system from Northern Digital, Inc. When the normal monkey was tested at higher speeds, the locomotion pattern changed from walking to jogging. Within the 0. 4-0. 9 m/s range, stride length increased from ≈0. 06 to 0. 13 m in the normal animal, while stride frequency was ≈1. 0 Hz at all walking velocities. This is similar to previous studies that demonstrate that an increase in walking velocity is predominantly based on a longer stride length rather than

on changes in frequency of stepping. The accuracy of paw placement relative to the lateral portion of the chest did not vary much in this velocity range. The average paw placement was just under chest for walking velocities below 0. 6 m/s and only about 1 cm lateral at higher velocities.

A striking finding was that there was some dispersion in paw placement at lower velocities, but that this variability decreased as the animal walked faster. This paw placement relative to the body provides a metric for demonstrating the accuracy of walking. The pattern of locomotion was changed after canal plugging. The plugged monkey had visible problems in maintaining body stability. Its stride length was relatively long when walking at 0. 4-0. 6 m/s (≈0. 15 m) and increased further at 0. 9 m/s. The accuracy of paw placement at 0. 4 m/s was close to that of the normal animal, but as the canal-plugged animal walked faster, there was an increase in the variability of paw placement and the average position of the paw relative to the body shifted laterally by 4 cm, giving the animal a broad-based gait.

It is assumed that the vestibular system controls locomotion, but there is little information about the exact parametric measures that are altered after specific vestibular lesions. These data suggest that activation of the semicircular canals are important for maintaining accuracy of paw placement and lateral placement of the paws relative to the body during walking. (Supported by NIH Grants: DC04996, DC03787, DC03284, EY11812, EY04148, and EY01867)

**B4.1**

**The Effect of Acute Vertigo on Objective and Subjective Autonomic Measures in Dizzy Patients**

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Dizzy patients often complain of autonomic symptoms but such responses in acute vertigo have not been previously documented. Using questionnaires, blood pressure, pulse and respiration recordings during caloric testing of patients in a dizzy clinic, we document a case of vertigo-induced panic attack without nausea, a case of vertigo-induced migraine with anxiety and nausea, and for comparison, a case in which the only significant response to vertigo was that of nausea. Such reactions have not been previously documented. We discuss the utility of noting patients' reactions during acute vertigo induced by caloric testing.

**B4.2**

**Vestibular influence on the respiratory rhythm during active change of posture in human beings**

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To assess the vestibular influence on the respiratory rhythm during active change of posture, we evaluated 50 healthy volunteers (18 to 59 years) and 15 patients with peripheral vestibular lesions (18 to 55 years): 10 patients with acute vestibular neuritis and 5 patients with chronic, bilateral, vestibular failure. After 5 minutes of supine rest, subjects were asked to sit down for 5 min and then to stand up for another 5 min. Respiratory movements of the thorax and abdomen were recorded (Respitrace, NiMS), and analyzed off-line using commercial software (Respi-Events, NiMS). Repeatability of the respiratory measurements was evaluated on 10 healthy volunteers, and it showed to be higher than 90%.

In healthy subjects, after the change of posture from supine to seated, we observed a consistent decrease of the respiratory frequency (mean -0. 9 breaths per minute, S. D. 2. 5 for men and 1. 24 b/m, S. D. 2. 2 for women). This response was related to an increase of the expiratory time ($p< 0. 05$, ANOVA). However, during the same condition, in patients with vestibular neuritis we observed an increase of the respiratory frequency (mean 1 b/m, S. D. 2. 3), which was significantly different from the response of 10 age/sex matched healthy subjects ($p< 0. 05$, ANOVA). The labyrinthine defective subjects showed inconsistent changes, with a trend to increase the respiratory frequency.

We conclude that the vestibular system has an influence on the respiratory response to head movements in the saggital plane.

**B4.3**

**Cerebrovascular Response to Tilts in the Pitch and Roll Planes**

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The assumption of the upright posture results in a number of hemodynamic changes to maintain cerebral blood flow. Recently, extensive evidence has shown an important role for the vestibular system in these hemodynamic changes. However, little is known about the contribution of the vestibular system to cerebrovascular changes during the assumption of the upright posture. To address this question, healthy subjects experienced a series of tilts: 1) Supine tilted forward to an 80 degree head up position; 2) Prone position tilted to an 80 degree head up position; 3) Left ear down tilted in roll plane to an 80 degree head up position. We hypothesized that cerebral blood flow would be better maintained during supine tilt than either prone or left ear down tilts. Order of tilts were randomized with a minimum of 20 minutes supine between each tilt. Throughout the tilts, heart rate (ECG), blood pressure (finapres), cerebral blood flow velocity in the middle cerebral artery (transcranial Doppler) and end tidal carbon dioxide were monitored. Each tilt began with a 5 minute baseline, followed by 10 minute tilt and 5 minutes of recovery. Subjects demonstrated typical increases in heart rate (+12 ± 4 beats/min) throughout tilts that were greatest during left ear down tilt (+21 ± 3 beats/min, $P<0. 05$). While mean arterial pressure did not change significantly during tilt, a hydrostatically mediated decrease in blood pressure at the level of the eye was seen during all tilts (-20 ± 4 mmHg). Interestingly, even though upright blood pressure at eye level was similar across all tilts, suggesting similar cerebral perfusion pressures, subjects demonstrated significantly better maintenance of cerebral flow velocity during the supine tilt (-13 ± 4%) compared to the other two tilts (-18 ± 4%, $P<0. 05$). While decrease in

cerebral flow velocity differed between tilts, this could not be explained by changes in end tidal carbond dioxide since all tilts were associated with a mild hypocapnia (-2 ± 2 mmHg, P<0. 05). These results indicate that tilt position affects hemodynamic and cerebrovascular response to the upright posture. As hypothesized, tilting in the supine position resulted in better maintenance of cerebral blood flow than either the prone or left ear down tilts. These data support a possible role for vestibular activation in regulation of the cerebrovasculature during the upright posture. (Supported by NASA, NIH and Legacy Health Center. )

**B4.4**

**Vestibular Influences on Cardiovascular Regulation: An Overview**

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Some postural changes, such as standing from a supine position in humans or vertical climbing in quadrupeds, which place the long axis against the force of gravity can result in orthostatic hypotension. However, blood pressure rarely drops during postural changes because compensatory mechanisms produce a rapid redistribution in the blood volume. There is considerable evidence to suggest that the vestibular system participates in making rapid adjustments in blood pressure during movement. One line of evidence comes from experiments in which labyrinthine afferents were selectively stimulated.

Electrical stimulation of the vestibular nerves or head rotations in animals with extensive denervations to remove nonlabyrinthine inputs produced by the movement result in an increase in sympathetic nervous system activity and blood pressure. Only those sympathetic efferents that influence vascular smooth muscle, and not those that innervate targets such as gastrointestinal smooth muscle, respond to stimulation of the vestibular nerve. Furthermore, sympathetic efferents innervating blood vessels in the upper body and lower body often have opposite responses to vestibular stimulation. This finding is further supported by the observation that vestibular stimulation induces opposite hemodynamic responses in forelimb and hindlimb blood vessels. This work cumulatively indicates that the vestibular system provides complex, patterned influences on sympathetic nervous system outflow, and does not simply elicit nonspecific autonomic responses.

Other evidence showing that the vestibular system participates in cardiovascular regulation comes from studies in which labyrinthine inputs were removed and the effects of these lesions on orthostatic tolerance were assessed. Elimination of vestibular inputs diminishes the ability of an awake animal to rapidly adjust blood pressure during postural alterations. Effects of vestibular lesions on cardiovascular regulation are exacerbated by ablation of a specific region of the vestibulo-cerebellum: the uvula. These observations show that labyrinthine inputs participate in cardiovascular regulation during normal physiological conditions. (Supported by National Institutes of Health grant R01 DC00693. )

**B5.1**

**Results of vestibular rehabilitation after four weeks of a home program**

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Long and complicated vestibular rehabilitation programs to reduce vertigo and improve balance have been described in the literature. Few patients, however, appreciate having to attend the out-patient clinic for multiple visits. We describe here the results of a study of the effectiveness of a four-week home program of habituation exercises in which the patient increases the difficulty of the program to tolerance.

Fifty three subjects, divided into slow and fast head movement groups, were pre- and post-tested on level of vertigo, posturography scores, independence in activities of daily living, and spatial orientation. They did the home program for four weeks, and were post-tested at approximately monthly intervals for up to six months. Data were analyzed with multilevel analyses. Vertigo decreased significantly, and balance and independence improved significantly from pre- to post-test and then plateaued.

These data suggest that vestibular rehabilitation given as a home program can be effective in reducing symptoms and increasing independence in daily life tasks. (Supported by NIH grant DC02412. )

**B5.2**

**Posturographic Effects of Nicotine-Ethanol Interaction: Amplitude and Frequency Measurements**

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Prior studies from our laboratory have documented the negative effects of subintoxicating doses of ethanol upon postural stability in both amplitude and frequency measurements of sway during computerized dynamic posturographic (CDP) trials. These effects were most reproducible during Sensory Organization Test Condition 4 (SOT 4) trials with eyes open and support surface movement referenced to body sway. As part of the overall center project goal to identify genetic and environmental factors leading to alcoholism, we were interested in the effects of nicotine exposure upon posture control both in the presence and abscence of ethanol. Since epidemiologic evidence confirms that smoking and heavy alcohol consumption are closely related, we hypothesized that nicotine reduces the deliterious intoxicating effects of alcohol on posture control.

For this experiment, sixteen subjects (5 female, 9 male, ages 21-30 years) with a history of regular smoking and social alcohol consumption were tested using CDP under four test conditions in balanced order: 1) Placebo (no alcohol) alone, 2) Alcohol alone (peak blood alcohol concentration 0. 05 - 0. 06 mg/dl), 3) Placebo (no alcohol) plus cigarette smoking, and 4) Alcohol plus cigarette smoking. Both the amplitude-based SOT 4 score and Principal Components Analysis (PCA) of the 20 second sway spectra were analyzed.

Our results demonstrated the following: 1) Sway amplitude and 1 Hz sway energy was significantly increased with ethanol exposure, 2) Sway amplitude and 1

Hz sway energy was significantly reduced towards baseline levels with the addition of smoking to alcohol exposure, and 3) Smoking alone increased sway energy at 3-5 Hz which was reduced with alcohol exposure. In no case did smoking directly effect the blood alcohol concentration.

This study identifies significant effects of ethanol and nicotine upon postural stability and a strong interaction which may help explain the common coexistence of these two habits in the general population.

**B5.3**

**Protection of inner ear against acute environmental noise with antioxidants**

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Subjects exposed to discotheque noise may be predisposed to inner ear damage. Increasing evidence indicates that reactive oxygen metabolites (ROM) play an important role in the cell injury that follows intense noise exposure. ROM are free radicals, extremely reactive, and potentially cytotoxic. They directly destroy lipid membranes and DNA, and upregulate apoptotic genes, potentially leading to cell death. ROM are produced continuously as part of normal cell metabolism and are counteracted by endogenous antioxidant (AO) systems. No information of possible involvement of balance system exists. Experiments on guinea pigs have recently shown that administration of exogenous N-Acetylcysteine(NAC), an AO, provides protection from permanent hearing loss from acoustic overstimulation. The purpose of the present study was to evaluate whether exogenous AO can influence development of noise-induced TTS and in balance in humans.

Methods. A randomized study of 30 males (aged 20-30 yr) on the efficacy of AO to prevent discotheque noise-induced changes in the inner ear. Baseline hearing and balance measurements were made in a field clinic, adjacent to the discotheque. The subjects alternately received placebo or 400 mg NAC 1h before entering the discotheque. The noise level for each subject was monitored with personal noise dosimeters. The hearing was measured with clinical audiometry, starting with the left ear. The balance was measured on stable platform with virtual reality surrounding (VR). Also a stepping test was performed on posturography platform. Sway reference range, sway velocity and stepping pace as well as shift of centerpoint force was measured.

Results. After 4 h exposure noise dosimetry showed personal exposure levels of 92-94 dB The control subjects showed an average TTS of 8. 3 dB(L) and 10 dB (R) at 4 kHz, and between 0-3 dB at other frequencies. The TTS of the NAC treated subject did not differ significantly from the control subjects. In the VR-test the sway reference frame in forward direction and sway velocity differed statistically significantly between the placebo and NAC-groups. The NAC treated persons improved their balance

Conclusions. Although in animal experiments NAC effectively reduces permanent noise-induced trauma (PTS), in present experiments we could not demonstrate protection from TTS in humans. The mechanisms of TTS and PTS may be different and not depend upon ROM. So far, on the basis of these data, the "noise pill" still awaits invention. The balance function was significantly improved after treatment with AO, indicating possible beneficial effects of the antioxidants on vestibular function.

**B5.4**

**Contribution of vestibular apparatus to postural control during chair rise**

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It has been controversial how vestibular dysfunction affects postural control performance during daily life. Patients with bilateral vestibular hypo-function have been reported to show different linear control strategies from normal subjects during chair rise. Further, their angular control strategies depend on the condition of the vestibular apparatus.

In this study, we analyzed detailed angular change of body and head of the subjects with various kinds and degrees of vestibular dysfunction, using magnetic sensors. Our goal is to add some knowledge concerning the contribution of vestibular apparatus to the postural control of body and head when rising from a chair, which is a common action during daily life.

Materials and methods. 14 subjects with various degrees of peripheral vestibular hypofunction (PVH), 7 subjects with central disorder (CD), and 24 normal controls were included in this study. In PVH subjects, 8 presented with unilateral vestibular loss, 2 with complete bilateral vestibular loss, and 4 with incomplete bilateral loss with caloric testing. Magnetic sensors were placed on the back of the body and head of the subjects, and beside the flat chair, to refer the direction of the earth gravity. Subjects were instructed to sit on the chair with their feet slightly apart, and then to rise at their preferred speed, with their hands on their sides, not touched with any part of their body. Linear and angular head and body movements were measured for each subjects in two ways, with their eyes open and closed.

Results. Angular head movements relative to gravity were less in unilateral PVH patients than normal subjects. It is verified in another way that the rate of angular head-body movement against angular body-gravity movement tended to be larger in unilateral PVH patients. This appeared distinct with their eyes closed. This inclination became evident in bilateral PVH patients. On the other hand, we failed to find correlation between the value of caloric weakness and angular head movement in unilateral PVH patients. The results in CD subjects seemed to distribute between those in normal and PVH subjects. Linear head movement was also diminished in PVH and CD subjects.

Conclusion. The results suggest that the vestibular apparatus contributes to refer the direction of earth gravity, and align one's head to earth gravity, as well as to fix the horizontal position of the head.

**B5.5**

**Three Dimensional Analysis of Dysequilibrium in Cases with Unilateral Vestibular Disorders**

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Although some patients with unilateral vestibular disorders, even in compensated stage, complain dizziness/unsteadiness in daily life while putting on clothes, walking on a rough surface, driving, etc. , conventional equilibrium examinations are not enough to detect abnormality corresponding to the symptoms.

The purpose of this paper is to detect dysequilibrium in chronic unilateral vestibular disorders by use of a three dimensional video imaging method.

Method. In order to record body movements, reflective markers are placed on the bilateral head, shoulder, hip and knee joint of a test subject. The body movements are recorded by two video cameras, which are located so that the lines from each camera cross at the center of testing space. The marker positions in three dimensional co-ordinates are sampled to the computer in each video frame, 60 Hz, by off-line procedures.

Six healthy test subjects and four patients with chronic unilateral vestibular disorders, the conventional equilibrium examinations of whom indicated almost normal except canal paresis of the affected ear by the caloric test, were tested by the following trials: For healthy subjects, 1. Stepping with eyes closed, 2. Stepping just after rotary stimulation (1Hz, 3 times) to induce vertigo. For patients, 1. Stepping with eyes closed. In this study angle of rotation (AR) in relation to the vertical axis between the head and shoulder were analyzed.

Results. In the healthy subjects, middle correlation and standard errors between AR of the head and shoulder were observed during stepping. On the other hand, in the stepping after rotary stimulation, the correlations were extremely high and the standard errors, low. The result indicated that the movements of head and shoulder during stepping became very stiff as if they were fixed, by the induced vertigo. The results of patients with unilateral vestibular disorders were quite same as that of the healthy subjects during stepping with induced vertigo.

Discussion. This method is considered to be useful in detecting abnormality of chronic unilateral vestibular disorders, which could not be detected by the conventional methods.

**B5.6**

**Dimensional analysis of the vestibular labyrinth of the Brachiosaurus brancai**

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In all known vertebrates the vestibular system contributes essentially to the task of spatial orientation and sensorimotor co-ordination. To this end, the dimensions and neurophysiological circuitry in each species is optimally matched to its natural behavioural repertoire.

Earlier studies have indicated that the structure of the labyrinth - characterised by the three near-orthogonally arranged semicircular canals – was existent in species at least 100 million years old. The preparation of the fossilised labyrinth of a Brachiosaurus (courtesy of the Natural History Museum, Berlin) demonstrates that this structure predominated throughout the dinosaur age (i. e. more than 150 million years ago).

The dimensional analysis of this fossilised labyrinth permits an estimate of the frequency range of head movements. While the radius of curvature of the bony canal can be measured from the specimen, the internal radius can only be estimated on the basis of a number of assumptions. The results indicate that the natural frequency range for the semicircular canals was lower than that of existent (smaller) species, i. e. of the order of 0. 02 to 0. 1 Hz. This would support the idea that head movements of the brachiosaurus were considerably slower than those of existent species.

In addition, extrapolating from the allometric data collected and modelled in the studies of Jones& Spells (1963), an estimate of the body mass of the brachiosaurus can be made. This extrapolation yields a body mass in the order of 50 – 80 metric tons.

The reported study is embedded in a more comprehensive palaeontological reappraisal of the entire skeleto-muscular apparatus of the fossilised remains of the brachiosaurus.

**B6.1**

**Changes In Angular VOR After A Single Dose Of Intratympanic Gentamicin For Ménière's Disease**

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We studied the angular VOR in response to manual head thrusts using magnetic search coils before and after administration of a single intratympanic dose of gentamicin in 12 subjects with unilateral Ménière's disease (MD). We compared their gains to those of 5 normal subjects and 9 subjects who had surgical unilateral vestibular destruction (S-UVD). Horizontal head thrusts were used to excite the horizontal canals (HC), and head thrusts in diagonal vertical planes (45º from sagittal) were used to excite anterior (AC) and posterior (PC) canals.

Prior to treatment, MD subjects had horizontal (hVOR) gains indistinguishable from those of normal subjects (0. 93± 0. 17). After a single intratympanic gentamicin treatment, hVOR gains for head thrusts exciting the treated HC decreased to 0. 39±0. 11, significantly lower than pretreatment values ($p<0.001$), yet not as low as the gains from S-UVD subjects (0. 25±. 0. 09, $p=0.005$). Similarly, gains for head thrusts exciting the treated AC dropped from 0. 75±0. 22 to 0. 43±0. 14 ($p=0.006$), and for head thrusts exciting the treated PC, from 0. 82±0. 10 to 0. 37±0. 13 ($p=0.001$).

The results suggest that a single dose of intratympanic gentamicin markedly reduces the function of each semicircular canal on the treated side. The higher gain values obtained after gentamicin treatment compared to S-UVD suggest that gentamicin may cause a physiologically different lesion than S-UVD. Reasons for such a difference may be incomplete hair cell loss or preservation of resting vestibular afferent activity after intratympanic gentamicin treatment. (Supported by NIH R01 DC05040 and K23 DC00196)

**B6.2**

**Mechanisms of low pressure pulse technology in Meniere's disease - How does it work?**

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Clinical studies have indicated that application of middle ear pressure pulses in patients with Meniere´s disease can reduce vertigo spells, improve hearing and functional disability. Animal experiments have demonstrated that alternating pressure changes can induce a pressure change in the inner ear fluids which is dependent on the inner ear pressure regulation pattern and on the parameters of the applied pressure. In the course of these studies, certain properties of a pressure pulse have been defined that have proved to be most effective in reducing symptoms in patients with inner ear symptoms due to Meniere's disease.

A critical amount of kinetic energy in the pressure pulse seems to be necessary to induce a change in the hydrodynamic conditions in the hydroptic ear. Objective measurements of cochlear function using transtympanal electrocochleography have shown changes in the cochlear electric potentials indicating an immediate decrease in distention of the endolymphatic compartment and improvement in synchronisation of the cochlear electrophysiologic response - in direct relation to middle ear pressure applications. The key to the improvement seems be a decrease in hydrops.

Since the pathogenesis and mechanisms of vertigo spells remain unclear the mechanisms responsible for the reduction in spells can not be fully understood. Mechanisms which may be responsible for this improvement are discussed.

The clinical body of experience today of low pressure pulse treatment opens up various questions:
- optimal frequency and pressure amplitude in different patient groups?
- do pressure pulses activate a longitudinal and/or a circular fluid flow?
- any direct effects on the neurotransmittors within the inner ear?
- a functional correlation between the middle and inner ear pressure regulating systems?

**B6.3**
**Vertigo Response Patterns to the Meniett$^{tm}$ Device**
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The effectiveness of the Meniett$^{tm}$ device has been demonstrated in clinical trials.
However, the mechanism of its effect is not understood. The rate of vertigo control of people with Meniere's disease to the Menietttm device was evaluated using a daily symptom report card to delineate response patterns. It was reasoned that the rate of response would reflect the effect of the device on the pathophysiology of the disorder. If redistribution of endolymph were taking place, rapid responses would be anticipated; whereas if some other mechanism were involved to decrease endolymph production, slower responses would be expected.

The patients scored their vertigo intensity each day on the symptom report card. These scores were summed for each month of followup and plotted. About 50% of cases experienced a rapid fall in vertigo frequency and intensity over the first 4 weeks, whereas 40% of cases had a notably slower response rate, and 10% of cases responded poorly.

These observations suggests that more than one response mechanism is involved in vertigo control with the Meniett$^{tm}$ device. (Supported by the Virginia Merrill Bloedel Hearing Research Center)

**B6.4**
**The Preliminary Results of Endoscopic Removal of the Endolymphatic Sac in Ears Affected by Meniere's Disease**
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Since October 2000 , 18 endolymphatic sacs have been removed using an endoscope in ears affected by Menière's disease. At the time of writing the abstract (June 2002), only one of these ears has suffered any further vertigo. All the ears preoperatively showed abnormal summating potentials on electrocochleography and all the patients had a definite Meniere's disease according to the AAOO HNS criteria.

The author and a colleague proposed a drainage theory to account for the attacks of vertigo occurring in Menière's disease. Since 1991, the endolymphatic sac has been removed in 161 ears affected by Menière's disease. Using AAOO HNS criteria: group A results were obtained in 59% and group B (substantial) in 25%. The longterm results in patients ( n 42) who had initial good results (group A ) have been favourable with a longterm recurrence rate of vertigo of only 5% during a 2- 9 year follow up.

Two ears (2/161) have suffered a catastrophic loss of hearing. In each case the vertigo was not severe and the patients were discharged home on the first post-operative day with only mild imbalance. Although this feeling of imbalance increased on the 2nd and 3rd days, neither sought a further consultation and the loss of hearing was only confirmed at the routine follow-up appointment.

Endoscopy has added a new dimension as it is easy to see if any of the external sac remains after extirpation. It would appear that unless an endoscope is used, it is common to leave behind part of the sac and this may account for the failure to adequately control the vertigo in a few cases. Video of surgery will be used to illustrate the technique.

**B6.5**
**Vestibular Rehabilitation After Transtympanic Gentamicin Administration**
**K. R. Gottshall**, M. E. Hoffer, R. J. Moore, R. D. Kopke, D. Wester
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Transtympanic gentamicin is a popular treatment modality for vertigo associated with Meniere's Disease. Despite the popularity of this treatment and the known transient unsteadiness, which can accompany this treatment, the impact of vestibular rehabilitation on this patient group has not been well documented. We present our experience with sustained release administered gentamicin and vestibular rehabilitation therapy.

Forty-two patients were treated with the Round Window Mircocather between July 1997 and April 2001.

Twenty-eight patients underwent vestibular rehabilitation and 14 received no vestibular rehabilitation. The patients who received rehabilitation were treated with a battery of vestibular-ocular reflex, somatosensory, and positional rehabilitation exercises. All patients experienced transient post-surgical unsteadiness. The degree and length of this disability was significantly better in the patients who underwent rehabilitation than in those who did not receive rehabilitation.

The Dizziness Handicap Index was improved and posturogarphy normalized in all patients who underwent rehabilitation. Transtympanic drug therapy has become an important modality in the treatment of Meniere's Disease. The need and utility of a short course of vestibular rehabilitation to improve patient outcome is an important correlate to this therapy.

**B6.6**

**Intratympanic Gentamicin in Ménière's disease**

**N. Perez**[1], E. Martin[2]

*[1]University of Navarra, Pamplona; [2]Clinica de la Salud, Valencia*

Objective: This study aimed to analyze the results of the intratympanic injection of gentamicin as a treatment option for the unilateral Meniere's Disease (MD) who are refractory to medical treatment.

Study Design: A prospective study using transtympanic gentamicin was begun in 1996.

Setting: Tertiary medical center

Patients. 71 Patients with unilateral Meniere's Disease according to the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) guidelines (1995), that were unresponsive to medical therapy for at least one year.

Intervention: Intratympanic injection of a prepared gentamicin concentration of 27 mg/ml were injected at weekly intervals until development of spontaneous nystagmus, Head-Shaking induced nystagmus or head-thrust sign indicative of vestibular hypofunction in the treated ear.

Main Outcome Measure: The 1995 AAO-HNS criteria for reporting treatment outcome in MD were used. The results of treatment were expressed in terms of control of vertigo, disability status, hearing level, quantitative measurement of vestibular function with caloric and rotatory chair test, and Sensory Organization Test of dynamic posturography. The patients degree of overall impairment was also evaluated by the Dizziness Handicap Inventory (DHI) and the UCLA Dizziness Questionnaire (UCLA-DQ).

Results: Vertigo was controlled in 83.1% of the 71 patients. Hearing loss as a result of gentamicin injection occurred in 23, 9, 11 patients at the end of treatment, three months after the treatment and two years after the treatment respectively. Recurrence of vertigo spells after initially complete control was noted in 17 patients. Vertigo in 13 of these patients was cured by another course of intratympanic injections of gentamicin.

Conclusions: Ending weekly intratympanic injections when clinical signs of vestibular deafferentation appear can control vertigo in the majority of the patients, and it is a useful alternative to surgical options.

**B7.1**

**Hair Cell Regeneration: A 21st Century Approach**

**E. W. Rubel**

*University of Washington, Seattle, WA*

As we enter the age of molecular medicine, it is important to work toward therapies the take advantage of modern breakthroughs in cellular and molecular studies of the vestibular system. One such potential breakthrough is the discovery of hair cell regeneration in the inner ear of birds. In view of the remarkable conservation of peripheral vestibular system structure and function throughout vertebrates, it would seem possible to parlay the discovery of cellular mechanisms responsible for hair cell regeneration in birds into an effective therapy for hearing and balance disorders of peripheral origin.

This presentation will have three parts. A brief summary of the history and current state of understanding of the cellular processes underlying hair cell regeneration in avian and mammalian inner ear will be followed by a review of studies examining the recovery of vestibular reflexes in birds as a function of hair cell regeneration. For example, in collaborative studies with the Fuchs laboratory, we have shown virtually complete VOR recovery following ototoxic drug damage that is dependent on visual experience as well as hair cell regeneration. Finally, I will discuss the potential and the barriers for the application of hair cell regeneration to vestibular rehabilitation after inner ear injury in man. (Support provided by NIDCD and the Oberkotter Foundation. )

**B7.2**

**Engineering and Biomedical Aspects of Vestibular Prostheses**

**C. Wall**

*Harvard Medical School, Boston, MA*

Recent technological and biomedical advances now make it feasible to produce miniaturized sensory, signal processing, and stimulus delivery systems that are roughly analogous to the cochlear implant but which provide information about self motion, instead of sound.

Despite these encouraging advances, many areas require work before balance prostheses become a reality. These include: (1) Developing a motion sensor array including miniaturization of sensors, reduction of power consumption and use of biocompatable materials; (2) Converting the sensed motion into physiologically meaningful information including sensory coding, design of the stimulus delivery system, development of appropriate animal models to validate these, and the consideration of non-implantable approaches; (3) Delivering the transformed information to the CNS taking into account the effect of disease process upon the site of stimulation, and the development of practical surgical approaches for implantable prostheses; (4) Facilitating vestibular deficient individuals to use the motion information by proper tuning of the implant to the individual, and proper training and rehabilitation; and (5) Assessing the device including evaluation of prosthesis efficacy plus its side effects, safety and ethical considerations, and FDA approval.

The development of an effective, implantable, vestibular prosthesis for clinical use in humans will probably require at least 10 years. While it is impossible to

predict future results and future research directions, there do appear to be some logical research steps that may lead to the development and clinical use of a prosthesis. Three of these issues are considered below.

Staging the Number of Stimulation Channels. Because semicircular canal responses are better understood that otolith responses, it is logical to begin by developing and testing a semicircular canal prosthesis. A next step might be to expand from one dimension of rotational stimulation to cover all three rotations. A next step might involve development of stimulation to replace the otolith organs. The otolith organs are not innervated by nerve branches that represent a single dimension of space, like the semicircular canals, and thus need a more complicated form of electric stimulation.

Parallel development of electric and sensory substitution prostheses. The potential demand for electric and sensory substitution versions of a prosthesis are probably very different. The possible benefits from each version are also quite different. A sensory substitution prosthesis (for example, a vibrotactile one) will probably be quicker to implement clinically because less invasive human experiments, which take less time to implement, can be used. Since both versions of a prosthesis would use the same motion sensors and digital signal processors it is logical that much of the hardware development will be done using the sensory substitution version of the prosthesis and then be transferred to the development of the electric device.

Human Experimentation. A number of ethical and practical concerns must be addressed prior to surgical electrode implantation specifically for human vestibular studies. These include: response adaptation to continuous electric stimulation, bilateral versus unilateral implantation of stimulating electrodes, and proof of concept for single ampullary nerve bundle stimulation.

**B8.1**

**Vestibular System as a Vertical Orientation Reference for Trunk Stability in Postural Control**

**F.Horak**

*Neurological Sciences Institute of Oregon Health and Science University, Portland, WA*

Studies showing minor effects of bilateral vestibular loss on postural response latencies and patterns in response to perturbations suggest that vestibulospinal reflexes are unlikely to be a very important mechanism for vestibular control of postural stability. However, studies on the effects of galvanic vestibular stimulation in standing subjects show that altering the symmetry of vestibulospinal activity results in trunk tilt and alters the final equilibrium position for automatic postural responses. Thus, we hypothesize that a critical role of the vestibular system in postural control is to provide an internal reference for vertical orientation of the trunk in space, especially when the surface is unstable.

Two studies examined the effects of varying frequencies of sinusoidal 1) translations (0.1-1.25 Hz) and 2) rotations (.01-.4 Hz) of the support surface in the saggital plane on postural stability in six subjects with bilateral loss of vestibular function and age-matched control subjects. We also tested the ability of vision and light touch of a finger-tip to substitute for vestibular information for postural stability.

The gain and stability of trunk displacement/surface displacement was significantly larger in subjects, particularly at the higher frequencies of displacement when healthy subjects stabilized their trunks with respect to gravity. At lower frequencies, both healthy and control subjects stabilized their trunks with respect to the support surface and there were fewer differences between vestibular loss and control subjects. Control subjects, but not vestibular subjects, demonstated rapid adaptation of the center of pressure forces during repeated exposure to the same frequency oscillation. Vestibular loss subjects used a strapped down head strategy with large pitch amplitudes unlike control subjects. Three of the 6 vestibular loss subjects were able to use vision to reduce trunk instability to within normal limits in response to surface translations, whereas 3 subjects were unable to substitute vision and showed the largest trunk instability. Despite significant trunk and head instability, the leg muscle activation patterns were normal in patients with vestibular loss as if it was driven primarily by surface characteristics. All vestibular loss subjects could substitute less than 100 grams of light fingertip touch an a stationary surface for loss of vestibular function to stabilize the trunk in space to within normal limits on the oscillating surface. However, subjects with vestibular loss were unable to stabilize their fingers in space on an oscillating surface, unlike control subjects.

These studies show that vestibular, visual and light touch information are important for providing an external reference for vertical orientation when subjects balance on an unstable surface. These sensory references for trunk stabilization in space appear to become increasingly important, the faster the surface oscillation. The ability to substitute vision for loss of vestibular function for postural stability may dependent more on the ability to centrally compensate than the ability to substitute light touch on a stationary surface. Supported by NIDCD DC01849.

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**B8.2**

**Homeostatic plasticity of central vestibular neurons after unilateral labyrinthectomy**

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Unilateral labyrinthectomy results in major oculomotor and postural disturbances that regress in a few days during vestibular compensation. The long-term consequences of unilateral labyrinthectomy were investigated after one month by characterizing the static and dynamic membrane properties of deafferented vestibular neurons recorded intracellularly in guinea-pig brainstem slices. We compared the responses of the type A and type B cells identified in vitro to current steps and ramps, and to sinusoidal currents of various frequencies.

All deafferented vestibular neurons were depolarized by 6-10 mV compared to the cells recorded from control slices. Both their average membrane potential and firing

threshold were increased, which suggests that changes in active conductances compensated for the loss of excitatory afferents. The proportion of type A neurons and the after-hyperpolarisation of the remaining type B neurons were significantly increased, both of which should stabilize the tonic discharge recovered in the deafferented nucleus. The deafferented type B cells became more sensitive to current injections over a large range of frequencies (0. 2-20 Hz), which might underlie the partial compensation of the dynamic vestibular reflexes observed in vivo. This was associated with an extension of the linear frequency response range of type B neurons, which might reduce their capacity to act as non-linear signal detectors and thus explain why responses to high amplitude velocity steps stay permanently impaired in lesioned animals.

In accordance with the top-down hypothesis we proposed recently, long-term vestibular compensation seems to involve major homeostatic changes in the membrane properties of the deafferented vestibular neurons.

**B9.1**

**Signal transmission between first and second order vestibular neurons**

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All hair cells in the crista of a given semicircular canal have the same direction of functional polarization. And yet, thousands of afferent fibers mediate their signals to the brainstem. These vestibular nerve afferent fibers differ among each other in a number of interrelated morphological, histochemical, and physiological properties. Fiber size-related differences in immunoreactivity, in the regularity of the resting discharge and in the phasic-tonic response pattern correlate with the spatial innervation pattern in the sensory epithelium, but not with the presence (mammals) or absence (e. g. frog) of type I hair cells. Even though the response properties differ in a graded and continuous manner between different caliber afferent fibers, thicker vestibular nerve afferent fibers tend to represent a particular subpopulation. Signals from thicker and thinner vestibular nerve afferent fibers converge onto second order vestibular neurons, but the transmission of these signals is one of the distinguishing features. Thicker vestibular nerve afferent fibers terminate with mixed synapses in non-mammalian vertebrates and in rats. These synapses are characterized by the presence of gap junctions for electrical transmission and of conventional synaptic contacts for chemical transmission.

The putative transmitter of vestibular nerve afferent fibers is glutamate/aspartate. In addition, glutamate and substance P are colocalized in thinner and glutamate and glycine in thicker vestibular nerve afferent fibers. The colocalization of the latter and a high affinity uptake mechanism for glycine in the largest vestibular nerve afferent fibers is compatible with the presumed synaptic release of glycine and its role as a cotransmitter. Postsynaptic AMPA/kainate receptors are activated by essentially all afferent nerve fibers. Thicker vestibular nerve afferent fibers activate in addition NMDA receptors. The activation of NMDA receptors is conditional. It is facilitated by electrical and AMPA receptor-mediated depolarization and by the occupation of the strychnine-insensitive glycine binding site. However, this monosynaptic excitation of second order vestibular neurons via NMDA receptors is restricted by inhibitory side loops.

Thick vestibular nerve afferent fibers activate second order vestibular neurons as well as local interneurons which inhibit the former neurons via GABA and/or glycine receptors. This feedforward inhibition is specific for signals from thicker vestibular nerve afferent fibers and allows for a graded control of the phasic-tonic response properties of second order vestibular neurons.

**B9.2**

**Regulation of firing in vestibular nucleus neurons**

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The gain and dynamics of vestibular reflexes are influenced strongly by the firing properties of vestibular nucleus neurons. To identify potential targets of pharmacological therapies that could affect vestibular function, we investigated how ion channels regulate firing response gains in vestibular nucleus neurons. Experiments were performed in rodent brainstem slices using a combination of electrophysiological and pharmacological techniques. Vestibular nucleus neurons fired spontaneously in brain slices. In response to inputs of increasing strength, firing rates increased in a linear fashion. Firing response gains (slope of the input to firing rate relationship) varied widely across vestibular nucleus neurons but were quite stable over the course of a recording session.

Pharmacological blockade of calcium channels and of calcium-dependent potassium (K-Ca) channels evoked dramatic increases in gain while having little effect on response linearity or dynamics. Pharmacological occlusion experiments revealed that N-type Ca channels influence gain via apamin-sensitive K-Ca channels, while T-type Ca channels affect gain via BK channels. Surprisingly, firing response gains increased following blockade of calcium-dependent calmodulin kinase II (CamKII), indicating that CamKII actively regulates gain. These results suggest the possibility that kinase modulation of ion channels in vestibular nucleus neurons could modulate vestibular reflexes in subjects with vestibular dysfunction.

**B9.3**

**Integration and non linear properties of the vestibular and prepositus hypoglossi neurons**

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Based upon their properties, three distinct neuronal cell types were found in the vestibular nucleus (VNn): the A, B and B+LTS cell. In the in vitro whole brain preparation, synaptic potentials could trigger subthreshold plateau potentials and/or putative low-threshold spikes in type B VNn. These non-linear, voltage-dependent events may have important physiological roles. Temporal summation of the long-lasting plateau potentials could be a substrate for the velocity storage integrator, which

lengthens the time constant of VNn discharges. Moreover, both the plateau potentials and the low-threshold spikes are often accompanied by superimposed bursts of spikes. This property could be used in vivo to synchronize the discharges of the VNn.

Whereas the same cell types were recorded in the prepositus hypoglossi nucleus, a fourth one had unique characteristics and was recorded solely in that nucleus. It is endowed with a highly 4-aminopyridine-sensitive current, which activates in the subthreshold range and inactivates slowly over time. The characteristics of this current, most likely an ID outward potassium current, suggest that it could, as originally suggested to be the case in hippocampal neurons, enable these neurons to integrate separate depolarizing inputs over long periods of time.

**B9.4**

**Cerebellar Control of the Vestibular System : A Pharmacological Study**

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Several lines of evidence have suggested that both nitric oxide (NO) and acetylcholine (Ach) are possible neurotransmitters/neuromodulators involved in lesion-induced vestibular plasticity. However, details of the effective sites during vestibular compensation remain unclear, because of their widespread location in the central nervous system. In the present study, we gave selective NO-inhibition or Ach-elimination in the rat vestibulocerebellar neural circuits by means of local injection of their inhibitors into the vestibulocerebellum. In these treated animals, unilateral labyrinthectomy (UL) caused much more severe vestibulo-ocular deficits, especially at the initial stage. Moreover, at that stage, neural activities in the contralesional medial vestibular nucleus (contra-Mve) were much more activated (disinhibited) using Fos protein expression. All these findings suggest that both NO and Ach in the vestibulocerebellar neural circuits facilitate vestibular compensation by inhibition on the contra-Mve immediately after UL.

**B9.5**

**Improvement of downbeat nystagmus and postural imbalance by 3,4-diaminopyridine, a prospective, placebo-controlled study**

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Several drugs that primarily act on GABA receptors have been used with moderate success to treat downbeat nystagmus syndrome. These drugs are also known to have several side effects including vertigo and blurred vision. In a search for more effective agents with less side effects, we evaluated the potassium-channel blocker, 3,4-diaminopyridine (3,4-DAP) in a prospective, placebo-controlled study. 3,4-DAP inhibits the A-current, thereby improving axonal conduction of action potentials, as well as the IK1 potassium current of vestibular hair cells, thereby increasing the input resistance of these cells.

Ten patients with downbeat nystagmus due to cerebellar degeneration (5) or of unknown etiology were treated randomly for 1 day either with 20 mg 3,4-DAP tid or at least 1 week later with placebo or verum. Before treatment and 30 min after ingestion of the verum or placebo, video-oculography was used to measure nystagmus and posturography, to determine the postural imbalance by sway-path values.

3,4-DAP significantly reduced mean peak slow phase velocity (PSPV) of downbeat nystagmus in eight of ten subjects (mean ± SD of PSPV before treatment: 6. 6 ± 4. 5 degs/s, during treatment with 3,4-DAP: 2. 1 ± 0. 7 degs/s, $p < 0.05$, one-way ANOVA). It also decreased the sway-path values. In parallel the subjects had less oscillopsia due to involuntary retinal slip and felt more stable while standing and walking. Except for transient minor perioral paresthesia reported by three subjects, no other side effects were observed. The placebo did not have any measurable effect on nystagmus or postural imbalance.

The study showed that 3,4-DAP reduced fixation nystagmus and postural imbalance in eight of ten patients with downbeat nystagmus syndrome, while having only minor side effects. By virtue of its electrophysiological properties as a potassium channel blocker, 3,4-DAP could have two conceivable mechanisms of action: it could either augment the physiological inhibitory influence of the vestibulocerebellum on the vestibular nuclei and/or modify the resting activity of vestibular hair cells and/or the vestibular nerve.

**B9.6**

**Acetazolamide and the Familial Vertigo and Ataxia Syndromes: Clinical Response and Mechanism of Action**

**J. C. Jen**, J. Wan, R. W. Baloh
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Objective. To summarize our experience with acetazolamide in treating familial episodic vertigo and ataxia syndromes, and to present preliminary data on the mechanism of action.

Background. Acetazolamide is effective in treating multiple familial episodic neurological syndromes due to mutations in ion channel genes. The mechanism of action of acetazolamide is unclear, although response is associated with a normalization of cerebellar intracellular pH.

Methods. We performed a genotype/phenotype correlation in families with mutations in the calcium channel gene, CACNA1A, to understand how these mutations lead to episodic vertigo and ataxia, and how acetazolamide controls symptoms. Whether acetazolamide has a direct effect on the calcium channel complex or whether it modifies or normalized the mutant calcium channel through changes in Ph or K+ is being tested in vitro. Wild type and mutant calcium channels were expressed in COS7 cells and the effect of acetazolamide on channel activity was studied using whole-cell patch clamp recordings.

Results. Responsiveness to acetazolamide varied in families with different mutations in CACNA1A. However, there was also variability of response within some families with the same mutation. Preliminary data indicates that acetazolamide acts directly on wild type calcium channels to cause a hyperpolarizing shift of the voltage dependence

of activation, thus lowering the threshold for channel activation and increasing calcium influx.

Conclusion. Patients with mutations in CACNA1A have a variable response to acetazolamide. Efficacy in patients with loss-of-function mutations may be explained by enhanced activity of the wild type channel to compensate for the mutant allele.

**B9.7**
**Symptomatic drug treatment of vertigo**
**G M Halmagyi**
*Royal Prince Alfred Hospital, Sydney*

Flunarazine and betahistine are two of the most popular drugs for symptomatic control of recurrent vertigo attacks. Flunarazine is mainly a calcium channel blocker; not much is known about its actions at the single neuronal or sub-cellular level in the vestibular system. It has also been used for prevention of migraine headaches and as a second-line anticonvulsant. It suppresses the vestibulo-ocular reflex. Post-marketing studies have shown it to be of equal efficacy with betahistine in the prevention of vertigo. Its principal side-effects are depression and extrapyramidal dysfunction. More is known about the actions of betahistine which is a weak histamine H(1) receptor agonist and a more potent H(3) receptor antagonist. In the peripheral vestibular system it reduces vestibular asymmetry and increases end-organ blood flow. Centrally it upregulates histamine turnover and release by blocking presynaptic histamine H (3) receptors and induces H (3) receptor downregulation in the posterior hypothalamus and in the vestibular nuclei. Betahistine also reduces ampullary nerve resting discharge rate but has little effect on responses to mechanical displacement although it does reduce the gain of the vestibulo-ocular reflex. In cats betahistine facilitates recovery of posture and postural reflexes after unilateral vestibular deafferentation. Despite this a Cochrane database review has found insufficient high quality clinical trial data in support of the efficacy of betahistine in Meniere's disease (James AL, Burton MJ. Betahistine for Meniere's disease or syndrome. Cochrane Database of Systematic Reviews 2002).

**B10.1**
**The Coordination and Planning of Eye, Head, and Hand Movements in Natural Tasks**
**M. M. Hayhoe**
*University of Rochester, Rochester, NY*

We have examined the coordination of eye, head, and hands in several natural tasks. Observations of subjects making sandwiches suggest that motor planning is a ubiquitous aspect of performance. Fixation durations, eye-hand latencies, and the existence of "look-ahead" fixations suggest that it is necessary to preserve information about spatial structure that can serve as a basis for planning and targeting eye and hand movements. Both eye and hand (or arm) movements appear to use visual information acquired in fixations a second or two prior to the current action. This is in agreement with other observations of natural behavior by Land and colleagues. This finding is supported by a copying task in a virtual environment. Subjects target the old location of objects even when the objects have been moved to a new location. This shows that memory of spatial location of objects is used in saccadic targeting of those objects, even when the target is present in the peripheral retina. In this task, we also find that head movements are tightly linked with hand movements. Head and hand movements both precede the eye in large gaze changes by 200 msec (head) or 400 msec (hand). This early initiation of the head and hand movements may be an advantage afforded by the use of spatial memory. The correlation of head and hand may also allow the head to act as a reference frame for the hand movement in the freely moving observer.

**B10.2**
**Planning and Control of Eye-head Movements: The Way to Move**
**J. Van der Steen**
*Erasmus MC, Rotterdam*

Orienting responses are universal across all living species. Whereas species with immobile eyes (e. g. insects) use only head and body movements, in mammals (with mobile eyes) orienting responses consist of sequential series of motions of different body parts (eyes, head, trunk). This requires a precise control of the sequence of events with respect to timing and amplitude. This becomes even more critical in foveate animals and in humans. In these species the frontal placement of the eyes in the head places restrictions on the field of view. Thus, in foveate species planning of orienting eye and head movements becomes an important aspect of motor programming.

In this presentation I will discuss the relative role of several brain structures involved in eye-head coordination (cerebellum, brainstem, cortex) and compare the behavioural and dynamic aspects of eye-head coordination in mammals with laterally placed eyes ( rabbits, mice) with that of frontally eyed species (man, monkey). This will demonstrate that absence of panoramic view in frontal eyed species is compensated by highlevel control mechanisms, that show a considerable increase in flexibility of motor programming.

**B10.3**
**Mutual Interactions Between Eye and Hand Movements**
**P. van Donkelaar**
*University of Oregon, Eugene, OR*

In order to reach to a visual target in extrapersonal space the central nervous system must perform a complex sensorimotor transformation that allows the accurate generation of coordinated eye and hand movements. Part of this process appears to involve the exchange of signals between the oculomotor and manual motor systems. We have examined this issue by having subjects make coordinated eye and hand movements under a variety of conditions.

In a first set of experiments, subjects made pointing movements without vision of the hand accompanied by saccades of the same size or two or three times larger. Under such circumstances, the pointing movement amplitude increased as saccade amplitude increased despite the fact that both the eye and hand were directed at the same final target location. This result implies that a saccade amplitude signal is integrated into the planning of the pointing response.

To examine where in the brain this integration process takes place single-pulse transcranial magnetic stimulation (TMS) was applied to the posterior parietal cortex (PPC) to temporarily disrupt the processing occurring prior to the onset of the eye and hand movement. When TMS was applied over the PPC 100-200ms after target presentation, the influence of saccade amplitude on the pointing movement amplitude was decreased. This suggests that the PPC integrates oculomotor signals related to saccade amplitude into the preparation of the pointing movement.

In a second set of experiments, we have attempted to gain insight into the observation that the saccadic main sequence is altered by the generation of a limb movement. In particular, for a given amplitude, saccade velocity is increased and saccade duration is decreased when a pointing movement is also made to the peripheral target. The fact that the limb movement is typically initiated well after the saccade implies that an efference copy signal influences the planning of the saccade.

To determine whether this efference copy signal carries kinematic or kinetic information these two variables were dissociated by adding a known mass to the arm. Once subjects adapted to the mass, the influence of the pointing movement on peak saccade velocity was measured. The results showed that when the mass resisted the arm motion peak saccade velocity was greater than when the mass assisted arm motion. Thus, the efference copy signal that influences saccade planning appears to carry kinetic information related to the upcoming limb movement.

Taken together, these results demonstrate that there are mutual interactions between the oculomotor and manual motor systems during coordinated eye and hand movements. These interactions involve specific types of information and are carried out in specific regions in the brain.

**B10.4**

**Role of Sensory Information in Updating Internal Models of the Effector During Eye-Hand Co-ordination**

**J. Vercher**
*CNRS, Marseille*

In everyday life, eyes and hand movements appear to be closely linked (co-ordinated). We recently proposed a model of eye-hand co-ordination during self-moved target tracking. We will show some evidence about the use of proprioceptive information for updating internal models, which we believe to be involved in this co-ordination. Indeed, motor and afferent information contribute to the parametric adjustment (adaptation) between arm motor command and visual information about arm motion.

The study reported here was aimed at assessing the contribution of arm proprioception in building (learning) and updating (adaptation) these representations. The subjects (included a deafferented subject) had to make back and forth movements with their forearm in the horizontal plane, over learned amplitude and at constant frequency, and to track an arm-driven target with their eyes. The dynamical conditions of arm movement were altered (unexpectedly or systematically) during the movement by changing the mechanical properties of the manipulandum.

The results showed a significant change of the latency and the gain of the smooth pursuit system, before and after the perturbation for the control subjects, but not for the deafferented subject. Moreover, in control subjects, vibrations of the arm muscles prevented adaptation to the mechanical perturbation. These results suggest that in a self-moved target tracking task, the arm motor system shares with the smooth pursuit system an internal representation of the arm dynamical properties, and that arm proprioception is necessary to build this internal model. As suggested by Ghez et al. (1990), proprioception would allow control subjects to learn the inertial properties of the limb.

**B10.5**

**Predictive control of head, hand and eye movements: similarities and dissimilarities**

**G. R. Barnes**
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When human subjects track the motion of a visual target there is usually evidence of some attempt to predict target motion. This applies whether tracking with eyes alone (ocular pursuit), with head and eyes together (head-free pursuit) or with hand and eyes (oculo-manual tracking). It is not difficult to understand how prediction might be carried out with head and hand movements, since anticipatory smooth movements can readily be made at will. By contrast, smooth movements of the eye cannot normally be made with velocity more than 3-4deg/s in the absence of a moving target, making comparisons with head and hand difficult. However, it is now apparent that anticipatory smooth eye movements of much higher velocity (up to 30deg/s) can be made at will, given the right circumstances.

The critical factor that facilitates the volitional generation of smooth eye movements is the expectancy of forthcoming target motion. The technique we have used to elicit such movements is the remembered pursuit task, in which a timing cue is given at a fixed interval before the appearance of a target that moves at constant velocity for a set period of time. When this technique has been used to examine the responses to combined movements during head-free pursuit or oculo-manual tracking the anticipatory movements of head, hand and eye are found to be very similar. They are characterised by smooth movements that start some 200-300ms prior to target appearance and progressively increase in velocity as target onset approaches. This anticipatory velocity profile is quite different to that of the normal reactive response of head, hand or eye. An important aspect of such movements is that they are clearly of non-visual origin. Even in the eye, given the right expectancy, they can be made at any desired velocity (within limits), although they are normally graded on the basis of velocity coded information that appears to build up in a short-term store as a result of past experience. Evidence of this storage process can be seen if the expected target fails to appear, when predictive responses are released that represent the output of the stored information. Timing information is also stored as part of this process and is essential for timing the release of stored information. Although head, hand and eye do exhibit similar anticipatory behaviour, the release of such activity in combined activities does not necessarily occur simultaneously. In fact, as we have shown experimentally, predictive activity for head and gaze can even be made to occur in opposing

directions.

These findings point to a common mode of operation for tracking mechanisms, in which estimates of the required velocity of head, hand or eye movement are used to initiate a motor response in advance of feedback from visual information, thus overcoming delays in visual processing. Evidence suggests that visual feedback is maintained during this process, fine tuning the response and quickly correcting inaccurate estimates. Currently available evidence suggests the involvement of fronto-parietal cortical areas in this process of generating predictive velocity estimates.

**B10.6**

**Evidence of predictive activity for smooth gaze control in the caudal frontal eye fields of trained monkeys**

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Moving objects can be accurately tracked by smooth-pursuit eye movements. This system uses retinal image-slip-velocity information of the target to match the eye-velocity in space (i. e. gaze-velocity) to the actual target velocity. To maintain the target image on the fovea during smooth gaze-tracking and to compensate for the long delays involved in processing visual motion information and/or eye-velocity commands, the pursuit system must use prediction not only on the motor side as preparation and perseverance of ongoing movements, but also on the sensory and/or perception side about the direction and speed of the target movement (e. g. Barnes 1993). Caudal parts of the frontal eye fields (FEF) in the arcuate sulcus are known to contain smooth-pursuit neurons (e. g. McAvoy et al. 1991). Our recent observations show that the majority of such neurons carry retinal image-slip-velocity and gaze-velocity signals (Fukushima et al. 2000). To understand what role pursuit neurons in the caudal FEF play in predictive smooth-pursuit, we examined discharge characteristics of these neurons in head-stabilized macaques.

Our results, as summarized below, present evidence that these neurons indeed carry predictive signals for smooth-pursuit. When a stationary target abruptly moved sinusoidally along preferred directions at 0. 5 Hz, the response delays of pursuit neurons seen at the onset of target motion were compensated in next cycles. Only a quarter of a cycle was sufficient for this compensation. The monkeys were also required to continue smooth-pursuit of a sinusoidally moving target while it was blanked for about half of a cycle. This blanking was applied before cell activity normally increased and before target changed the direction. A majority of pursuit neurons discharged appropriately up to 500 ms after target blanking with normalized mean gain (re control value without blanking) of 0. 81. Similar results were also obtained during sinusoidal whole body rotation when the monkeys suppressed the VOR by fixating a target that rotated with them.

A majority of pursuit neurons tested also showed a predictive visual response. To test this, the monkeys were required to fixate a stationary spot while a second spot was moved sinusoidally. When the second spot moved abruptly, the response delays clearly seen at the onset of sinusoidal spot motion were compensated in next cycles. Blanking was also applied during sinusoidal motion of the second spot while the monkeys fixated a stationary spot. Preferred directions were similar and normalized mean gain of 0. 72 was still induced by the second spot motion during blanking. To examine the possibility that this visual response was due to a delayed response to retinal image-slip information presented during the remaining half of each cycle, we flashed the second spot sequentially as it moved. Similar responses were still induced.

These results suggest that the caudal FEF contains extracted visual components that reflect direction and speed of the reconstructed target image, signals sufficient for prediction of target velocity.

**B11.1**

**Steroid-responsive bilateral vestibulo-cochlear syndrome: Is there evidence for autoimmune disease?**

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We aimed to determine the diagnostic criteria for autoimmune disease in patients with rapidly deteriorating bilateral vestibulo-cochlear function. 15 patients with bilateral vestibulo-cochlear syndrome of acute or subacute onset were thoroughly examined for symptoms, signs, and laboratory findings of autoimmune disease. Clinical spectrum, clinical course, and response to steroid treatment were analyzed. Patients were grouped into: (a) Cogan syndrome (N = 6), (b) bilateral vestibulo-cochlear syndrome in association with multisystem and / or central nervous system manifestations (= "extended clinical syndrome", N = 4), (c) bilateral vestibulo-cochlear syndrome in isolation (N = 5). Exclusion criteria were: ototoxicity, bilateral Menière's disease, and infectious disease such as Lues, Borreliosis, and HIV.

Patients with Cogan syndrome and patients with an "extended clinical syndrome" were clearly steroid-responsive as documented by the stabilization or improvement of hearing. All these patients, when initially examined, showed signs of systemic inflammatory disease, such as increased erythrocyte sedimentation rate, increased C-reactive protein (CRP), leucocytosis, or meningitic cerebrospinal fluid (CSF). In contrast, patients without signs of inflammatory disease did not respond to steroid treatment. Laboratory tests indicative of autoimmune disease were slightly abnormal in only two patients (elevated ANA), both, however, showing no steroid response nor signs of inflammatory disease.

We conclude that the clinical and laboratory data indicating autoimmune disease in rapidly deteriorating bilateral vestibulo-cochlear syndrome are limited. Besides steroid-responsiveness, which alone is not a sufficient criterion, findings suggestive for autoimmune disease were: (i) Cogan syndrome or an "extended clinical syndrome", (ii) laboratory signs of systemic inflammatory disease, and (iii) meningitic CSF without signs of infection. - Rapidly deteriorating bilateral vestibulo-cochlear function without findings indicative of Cogan syndrome or an "extended clinical syndrome" may still be and probably is of autoimmune origin in some patients. Other diseases, that

also can be influenced by steroids, such as mitochondrial cytopathy, however, have also to be taken into consideration. (Supported by Swiss National Science Foundation (32-51938. 97 / 31-63465. 00) and Koetser Foundation for Brain Research, Zurich, Switzerland).

**B11.2**

**New Strategies in the Diagnosis and Treatment of Motion Sickness**

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Motion sickness is a common disorder that can have a significant impact on individuals who must work in a motion environment. The disorder is difficult to study since symptoms are only present under specific motion conditions and the symptoms can vary from severe nausea and headaches to minor fatigue. Screening programs for motion sickness have often relied on placing individuals in a specific type of motion and observing their response. Tests that could be performed in a standard laboratory setting and which could be used to guide therapy would aid investigators and clinicians who treat this disorder.

We report the results of a standard vestibular test battery performed on a group of active duty military individuals who were referred to our clinic for motion sickness. This battery included rotational chair testing, posturography testing, and high speed head rotation testing, as well as a customized vestibular physical examination. The results in this group were compared to an age and sex-match control group of patients.

While the control group had a less than 5% rate of abnormalities on standard balance testing, over 70% of individuals in the motion sick group demonstrated abnormalities on standard vestibular laboratory testing. The results of these test often correlated with the symptom complex and could be use to categorized the motion sick individuals. Targeted vestibular rehabilitation that was designed to treat the testing abnormality was successful in controlling motion sickness in a subset of these individuals.

We examine the implications of non-motion vestibular test abnormalities in motion sickness and discuss how such test results can be used to allow for successful treatment in many of these individuals.

**B11.3**

**Threshold of semicircular canal and otolith in galvanic stimulation**

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The Galvanic test has been studied as a test of equilibrium. However, it has been less applied clinically than other tests, partly because analysis of the ENG records is difficult due to the contamination by the electric stimulation. In this study, to overcome this problem, we recorded and analyzed galvanic nystagmus in healthy individuals using infared video-oculography.

The subjects were 14 healthy volunteers (8 males and 6 females; mean age 30. 8 years). Electrodes were taped to the mastoid processes of both ears. The right electrode was the cathode, and the left electrode was the indifferent electrode. Direct current stimulations at 1, 2, 3, and 4 mA each with a 30 second duration were applied using a direct current stimulator. Nystagmus was recorded with regard to the frequency of nystagmus and average slow phase velocity.

Nystagmus was evoked toward the cathodes in all subjects. The threshold of the response was 1 mA in 10 and 2 mA in 4 of 14 subjects. The average frequency of nystagmus was 0.645 Hz at 1 mA, 1.088 Hz at 2 mA, 1.348 Hz at 3mA , and 1.592 Hz at 4mA. The average slow phase velocity was 2.121, 5.053, 7.564, and 9.130 deg/sec, respectively. Both the frequency of nystagmus and average slow phase velocity tended to increase linearly with the intensity of the electric current.

Since nystagmus was provoked toward the cathode the cathodic current is considered to have increased the firing of the vestibular afferent pathway. Zinc et al. , who performed experiments using an infrared video-oculography and a similar stimulation pattern, reported that there was a difference in the threshold of evoking a response by galvanic vestibular stimulation of the otolith and semicircular canal. According to our results, nystagmus was evoked at 1-2 mA, and the threshold by galvanic stimulation is not considered to be different between the otolith and semicircular canal. The firing rate of the vestibular nerve is estimated to increase linearly with the intensity of electric current.

**B11.4**

**An Experimental Study of Vestibular Decruitment**

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Vestibular Decruitment (VD) is a paradoxical nystagmic response to thermal stimulation of the inner ear in which if two unequal stimuli are applied (the Torok monothermal caloric test) the weaker of the two elicits a greater response. Our clinical studies have shown that this finding correlates well with lesions of the brainstem and cerebellum. In order to study the neuropathological mechanisms of VD, the first question to be answered was whether VD could occur in a normal labyrinth. We addressed this issue by testing young normal healthy individuals with the above caloric test. We found that none of our normal subjects showed VD. However, we still needed to know whether the output of the labyrinth to thermal stimulation was linear and that it was not modified by the vestibular-ocular reflex. We attempted this experiment in cats but technical difficulties forced us to abandon this line of investigation. An elegant alternative was to use an in-vitro frog posterior semicircular canal preparation.

Experiments were carried out on whole frog labyrinth preparations isolated from the frog rana esculenta. The posterior semicircular canal together with its ampullary nerve was micro-dissected free. The preparation was then transferred into a chamber so that the posterior canal was laid in the vertical plane. The nerve-firing rate was recorded from the ampullary nerve by an electrode using a window discriminator. The ampullary receptors were stimulated with a heat probe and a current generator. The latter was controlled by a personal computer equipped with a homemade software program through its parallel port.

Stimuli consisted of square waves (40 to 120 second duration) at different intensities (0-20 ma). Our pilot study showed that the output from the frog labyrinth remained linear to increasing strengths of thermal stimulation.

The conclusion drawn from this study as well as from our evaluation of normal human subjects, is that the output of the labyrinth to increasing sensory stimuli does not result in the paradoxical response of VD. Based on these results, it can be presumed that VD is a central phenomenon and previous clinical studies have confirmed this finding in patients with MRI documented brainstem and cerebellar lesions.

**B11.5**

**The Video-impulse test enhances the possibility of detecting vestibular lesions**

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The vestibular head impulse test is useful to detect lesions of semicircular canals or vestibular nerve dysfunction. It may be performed with magnetic coil recordings system and by calculation of 3-D eye movements vertical canal function can be estimated. In clinical practice, the head impulse test is performed under inspection of the naked eye and often restricted to evaluation of the horizontal VOR. The test however, is less sensitive to detect partial lesions and according to Shepard a caloric side difference of about 57% is needed to ensure a pathological test outcome.

Methods. We introduce the use of head impulses on patients using video nystagmoscopy goggles with a mask (Synopsis®) that allows one eye to be uncovered and to fixate in lateral or medial gaze. The subjects would focus a mark on the wall at 1m distance to allow patients with presbyopsia clear vision. The other eye is covered with the CCD camera which generates a close up view of the eye on the video monitor, enhancing the possibility to detect a distorted VOR.

Results. 40 patients with a vestibular schwannoma was investigated pre-op and had varying degrees of reduced caloric function. The video impulse test was always pathological when the caloric function reduced to 48% and usually detectable at 40%.

Conclusion. : By observing eye movements with video nystagmoscopy it was possible to enhance sensitivity in a clinical setting.

**B11.6**

**A new system for legitimizing balance complaints**

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Many patients we see in our clinic are medico-legal patients and have what could be called "ulterior motives" to malinger or embellish their complaints. While it is important to identify the patient who is malingering, it is also important to recognize an abnormality, which may be subtle or atypical, but still represents genuine pathology.

After extensive investigation, many patients have results that show only non-specific abnormalities, and sometimes the CDP patterns are ones that are in fact reported in the literature as being indicative of a non-organic disorder. However we have come to suspect that some of these abnormalities are in fact representative of subtle vestibular disease. We see two distinct subgroups of medico-legal cases; true medico-legal cases (typically motor vehicle accidents) and work injured patients. This latter group is looked after with regard to medical care and income replacement by a Compensation system, and is not involved in legal suits as a consequence of their injuries.

We exposed both our groups of patients to Computerized Dynamic Posturography (CDP) protocol to detect malingering behaviour as outlined by Goebel and refined by Gianoli. Both these authors allude to deficiencies in their respective techniques for detecting malingering behaviour, and we have developed our own criteria for recognizing malingerers. Our new technique consists of a broader nine-point scheme in which each factor is weighted and scored accordingly. Our system incorporates assessment of aphysiological performance, but also assigns scores for attempts to take the opportunity to feign when presented with such an opportunity. Thirdly, it is suggested that a subjective "gut feeling" is a very powerful tool in a clinician's diagnostic armamentarium and we assign a score to such a gut feeling.

Waddell's signs for psychological factors in low back pain are utilized as a validated method for determining malingering behaviour, but the presence of one or even two positive signs of the five does not label a patient as a malingerer. In the same way as Waddell, we accept that there is often a gray area. We have evaluated all of our patients with the Gianoli criteria and we discuss the advantages and increased sensitivity of the scoring system we use.

A further aspect of assessment of the medico-legal patient is the strategies we use when we suspect a malingering attempt. Strategies range from re-evaluation without warning after a one hour break, to a confrontational approach where a patient is told that "we know you're capable of doing better and you'll just have to try harder". It is also important to recognize that some patients are not simply guilty of out and out "fakery", but are "genuinely" embellishing due to past experience of having minimal symptoms dismissed by physicians as not being genuine.

**B11.7**

**On the site of the lesion in acute unilateral peripheral vestibular dysfunction**

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Acute unilateral peripheral vestibular dysfunction can be caused by various clinical entities such as vestibular neuritis, labyrinthitis, sudden deafness with vertigo, Ramsay Hunt syndrome and so on. However, the site of the lesion is still somewhat controversial. Recently we reported that galvanic-evoked vestibulo-collic reflex testing is useful for differential diagnosis of the labyrinthine lesion vs. the retro-labyrinthine lesion in patients with an absence of click-evoked vestibulo-collic reflexes (Murofushi et al. 2002). We assumed that the application of galvanic-evoked vestibulo-collic reflex testing for patients with acute unilateral peripheral vestibular dysfunction could provide answers for questions concerning the site of the lesion in

these patients. Herein, we report results of galvanic-evoked vestibulo-collic reflexes in patients with acute unilateral peripheral vestibular dysfuntion.

Materials and Methods. Fourteen patients with acute unilateral peripheral vestibular dysfunction were enrolled. All of the 14 patients showed a unilateral absence of vestibulo-collic reflexes evoked by 95 dBnHL clicks and a unilateral absence of caloric responses by ice water. Their clinical diagnoses were vestibular neuritis in 8 patients, Ramsay Hunt syndrome in 4 patients, and sudden deafness with vertigo in 2 patients. We studied the average responses in the unrectified EMG of the SCM to galvanic stimulation (3 mA, 1 msec). The cathodal electrode was on the mastoid, and the anodal electrode was on the forehead. The stimulation rate was 5 Hz, and the analysis time was 50 msec. The responses to 50 stimuli were averaged twice with and without contraction of the SCM. To remove electrical artifacts we subtracted the average obtained without muscle contraction from the average obtained with muscle contraction.

Results. All of the 14 patients showed normal biphasic responses on the unaffected side. Among the 8 patients with vestibular neuritis, 6 patients (75%) showed an absence of galvanic-evoked vestibulo-collic reflexes on the affected side while 2 patients (25%) showed normal biphasic responses on the affected side. Concerning 4 patients with Ramsay Hunt syndrome, 3 patients showed biphasic responses on the affected side while one patient showed an absence of responses. Both of patients with sudden deafness with vertigo showed normal biphasic responses on the affected side.

Discussion and Conclusion. Galvanic-evoked myogenic potentials on the SCM were first reported by Watson et al. (1998). They also showed that this response disappeared after selective vestibular nerve section (1998). These results suggested that this response could be of vestibular origin. Murofushi et al. (2002) reported that this test is useful for differential diagnosis of the labyrinthine lesion from the retro-labyrinthine lesion in patients with an absence of click-evoked vestibulo-collic reflexes. We applied this test in patients with acute unilateral peripheral vestibular dysfunction. This study showed that the site of the lesion could be in the labyrinth as well as in the retro-labyrinth. So-called "vestibular neuritis" could consist of vestibular neuritis and vestibular labyrinthitis.

**B11.8**

**Study of VEMP in young adult dizzy patients of unknown origin**

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Disequilibrium caused by saccular dysfunction is suggested by physiological evidence. The saccule is the receptor of the linear acceleration, thus the disequilibrium may be caused by the changing gravity, for instance going up or down by the elevator. Also, the polarization vectors of the saccular neurons lay near the sagittal plane, thus the dysfunction might cause disequilibrium within the sagittal plane such as falling sensation to downward or backward. Those symptoms were tentatively called the sagittal symptoms in this paper. Saccular function has been evaluated by the vestibular evoked myogenic potential (VEMP) test. The patients who were diagnosed saccular dysfunction by VEMP may be included in dizziness of unknown origin (DUO). The purpose of this study was to clarify whether or not DUO included the saccular dysfunction.

We studied VEMP and clinical symptoms in young adult DUO to ignore arteriosclerotic changes and systemic aging. Subjects were 18 cases of DUO aged less than 40 years old at the neurotological clinic in Hyogo College of Medicine between 1999 and 2000. Their age ranged 24 to 38 (mean 29. 8) years old. DUO was diagnosed by the following criteria. They complained of non-roratory disequilibrium, however they had normal neurotological signs including the audiography, the caloric test, the eye tracking test and the optokinetic pattern test. They did not show any spontaneous, positional or positioning nystagmus. There were not any cerebeller signs or any intracranial lesions in MRI.

VEMP was measured by Neuropack 4 mini (Nihon Kohden, Japan) with 95 dBnHL click stimuli. During recording, the subjects were in the supine position and were instructed to keep their heads raised up and rotated to the opposite side. The results of VEMP were evaluated by the right-to-left ratio of n13-p23 amplitude. In our institute, the normal ratio was 1. 38 ± 0. 3 (mean ± SD), therefore the normal upper limit indicated 1. 98 (mean + 2SD). When the ratio exceeded normal range, VEMP data were considered abnormal.

Results. Abnormal VEMP were shown in 6 of 18 DUO cases. Each case complained of the saccular symptoms. Another 12 cases showed normal VEMP, although, the sagittal symptoms were shown in 5 of them. Sagital symptpms were related with results of VEMP (p=0. 025, Fisher's exact test).

Discussions. All cases who showed abnormal VEMP had sagittal symptoms, thus they were considered as dizziness due to saccular dysfunction. However, sagittal symptoms were seen in 5 of 12 cases with normal VEMP. Two reasons were suggested. First, disequlibrium in the sagittal plane was not thought to originate from only sacculus but also the posterior or anterior semicircular canal. Another was the sensitivity of VEMP results. Mild dysfunction of sacculus could show normal VEMP.

Patients with DUO included the dizziness caused by the saccular dysfunction. In these cases, the neurotological examination showed normal results except for VEMP. Therefore, VEMP test was suggested to be useful to diagnose DUO.

**B11.9**

**Dynamic Changes and Analysis of Electronystagmography for Unilateral Vestibular Peripheral Lesion**

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This study explores the characteristics, correlation and significance of electronystagmography (ENG ) in the different stages of vestibular lesion, compensation and convalescence after unilateral peripheral vestibular lesion. 150 such cases were reviewed, on whom were performed caloric, damped torsion swing test (DTST), head-shaking

nstagmus (HSN), spontaneous nstagmus (SN). 15 of these cases had a complicated course after reversible unilateral peripheral vestibular lesion, in which vestibular function fluctuated. After irreversible lesion, the course was simple and characterized by progressive functional improvement (i. e. compensation).

In different stages, ENG was presented with characteristic variations, multiple,non-unified contradiction forms. It was concluded that systemic and dynamic analysis of ENG characteristics was useful not only to determine which side the lesion was on but also to determine and monitor the course, central compensation and prognosis to help monitor the effectiveness of clinical therapy and vestibular rehabilitation training.

**B11.10**

**Development of a new generation force platform for the measurements of postural stability**

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A stable platform technique allows the measurement of postural deficiencies in a static situation only, where postural disorders usually show a good compensation. Dynamic situations that demand full compensation include body and head movements during various tasks. In such conditions posturography on a moving platform may reveal pathology better than static posturography. A tilt of the platform with simultaneously provided visual cues that can be synchronized or uncoupled from the movements of the platform may reveal the pathology behind postural instability better than the traditional techniques. The purpose of the present study was to develop a system that works as virtual reality (VR) platform. The paper focuses on technical detail on the system.

Construction of the platform: The platform has three pressure censors at the circle forming an equilateral circle. The signal from the strain gages is connected to datalogger (Hewlett-Packard 34790A, USA) sampling data at 150 Hz. The platform is supported from the middle point by ball pivot. Two motors can tilt the plate independently +-10 degrees in two directions under the control a programmable logic. The movement patterns are pre-programmed to the memory of the programmable logic and selected using binary control. This arrangement enables new kind of conventional and virtual measurements. In VR measurements the platform is moving with or without visual environment, or the test person is looking at moving scenery. We use virtual stereo glass (VR 8, Virtual Research, USA) to evoke the virtual visual environment. The resolution is 640X480 and a viewing angle of 60 degrees. The virtual views are developed using World Toolkit (Sense8, USA). The system is equipped with a head direction tracker (Intertrax 30, Intersense, USA) and the angle of the head affects to the viewpoint of the virtual scenery.

The test set up: The tests will start by determining the postural control range of the test person by: a) the determination of range of the extreme leanings forward-backward, left-right, b) target test where the test person should place the center point of body mass to the square that appears to the screen at five positions close to the ranges defined, c) the step test where the test person is asked to step on platform at constant speed, d) cone test where a rotating cylinder with accelerating speed appears in virtual helmet and provides circularvection, e) a tunnel test where moving tunnel appears in visual helmet. The movements of the VR are either synchronized or unsynchronized with the movements of the platform. For determination of postural stability several 180 different algorithms are under examination and from these the best oneswill be used. For practical analysis sway velocity and pace of body sway is displayed.

Conclusions. The VR platform has been used in several field studies. Mechanically the VR platform has been reliable. In testing repeatability within the same subject the results show a very good correlation. Still the best test parameters discriminating a healthy and disable person and the visual modes for VR stimulation must be searched for.

**B12.1**

**Decision Making In Visual Vestibular Conflict During Navigation: Role of the Hippocampus in High Level Integration of Spatial and Action Cues**

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During navigation the brain uses visual, vestibular and proprioceptive information to memorise paths. When asked to remember a travelled path, human subjects can use several cognitive strategies to recall their path ("route" involving the memory of kinesthetic cues, efferent motor signals, and "survey" involving map like memory of space). We have studied the memory of travelled path during a navigation task in which the subjects were wearing a visual virtual reality helmet and were sitting or standing . The rotations of their bodies was measured by a ultrasound angular position sensor. Their translations in the virtual world were controled by the computer but their rotations in the real world were controled by body rotations. This paradigm allows us to dissociate visual and vestibular or proprioceptive cues and also to change the gain and create conflicts .

The results of a memory task suggests that the brain does not only make a weighing of the conflicting inputs but actually " switches " betweeen them and makes a decision as to which sensor is to be " believed ". It is also possible that both visual and kinesthetic cues are stored in parallel and retrieved in a context and goal dependent manner. These experiments have also been made with patients with hippocampal lesions to understand the contribution of the temporal lobe to cognitive aspects of spatial disorientation. We have recently also demonstrated such a 'top-down" cognitive control in the determination of the subjective vertical in a conflict situation. (Mast et al. , 1999). In addition to providing fundamental knowledge about the brain mechanisms of spatial disorientation, this method can be used for the study of spatial anxiety and possibly for the rehabilitation of patients with spatial disorientation (Galati et al. , 2000;Mellet et al. , 2000)

**B12.2**

**Visual reference frame in postural control after unilateral vestibular loss**

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The aim of this study was to analyze the role of visual reference frame in head and trunk orientation and stabilization and their recovery after complete unilateral loss of vestibular information in humans. The ability of Ménière's patients to orient and stabilize their heads and trunks in space was investigated during a simple dynamic task of knee-bends with eyes open and eyes closed, and in static conditions under three visual contexts (light with and without vertical and horizontal coordinates, darkness). Patients' performance was recorded before unilateral vestibular neurotomy (UVN) and during the time-course of recovery (1 week, 1 month, 3 months) and compared with the performance of healthy subjects. Head and trunk orientation and stabilization in the roll plane and the yaw plane were recorded using a video motion analyzer system. Unilateral vestibular loss was responsible for postural deviations whose direction depended on the visual context, and specifically, on vertical and horizontal reference frames.

The results suggest that the underlying mechanisms for recovery of postural control include (1) a powerful impact of vision as shown by the visual-related deviations in the acute stage after vestibular loss, (2) a transitory behavioral substitution with head stabilization on the trunk after UVN, (3) a sensory substitution role of visual cues gradually decreasing over time, (4) a lack of total compensation by the remaining labyrinth 3 months after UVN.

**B12.3**

**The use of optic flow for the rehabilitation of visuo-vestibular symptoms**

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Visual vertigo symptoms are common in vestibular patients with unsuccessful compensation but the most effective rehabilitation method remains an open question. Forty chronic peripheral vestibular patients (28 females and 12 males, mean age: 44 years) who had previously undergone conventional vestibular rehabilitation (Cawthorne-Cooksey exercises) without notable improvement were randomly allocated into either a customised exercise regime (Group A) or a tailored rehabilitation program integrating whole-body or visual environment rotators (Group B). The latter creates sensory mismatch during the therapy. Individuals attended therapy sessions twice weekly for eight weeks and were provided with a tailored home program. Patients were assessed with computerised dynamic posturography and questionnaires about their symptoms, symptom-triggers and emotional status.

Final data shows that posturography and subjective scores significantly improved for both groups compared to baseline values, although Group B results tended to be better. Following treatment, anxiety and depression levels were significantly decreased for both groups. Autonomic symptoms improved to a greater extent for Group B than Group A ($p<0.01$). Scores for the Situational Characteristics Questionnaire, which largely assesses visually triggered dizziness, showed an overall improvement of 54% for Group B and 27% for Group A ($p<0.01$).

Conclusions: Both groups improve significantly, however, results indicate that treatment involving conflicting visual stimuli provides more positive results and therefore, must be incorporated as an integral aspect of vestibular rehabilitation.

**B12.4**

**Why Do Extraocular Muscles Have A Dual Innervation?**

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Unlike the skeletal muscles, the extraocular muscles contain non-twitch muscle fibres. Recent experiments have located the non-twitch motoneurons. They lie around the periphery of the oculomotor, trochlear and abducens nuclei, separate from the more usual twitch motoneurons, which cluster within the boundaries of the classical motor nuclei.

The premotor inputs to non-twitch neurons were traced by the injection of rabies virus into the distal tip of the lateral rectus muscle. Retrogradely labelled cells were found in areas associated with the neural integrator, vergence and smooth pursuit premotor areas, but not the saccadic premotor burst neurons or the direct, magnocellular vestibulo- ocular pathways. The rabies tracing also emphasise for the first time that the central mesencephalic reticular formation (cMRF) and the supraoculomotor area exert a direct premotor control over the non-twitch motoneurons. Since the two sets of motoneurons, twitch and non-twitch, do not receive the same afferents, they must have different functions: although these are not yet clarified. These results are not compatible with the concept of a single final common pathway from motoneurons to eye muscles.

Putative sensory receptors, palisade endings, are located at the tips of only the non-twitch muscle fibres - reminiscent of an inverted muscle spindle. If this analogy is followed further then it suggests that the non-twitch motoneurons function as gamma-motoneurons. We propose that twitch motoneurons are the major source of tension used for eye movements, whereas non-twitch motoneurons are more important for the tonic adjustment of muscle length, e. g. the alignment of the eyes. Furthermore the non-twitch motoneurons could be controlled through sensory feedback networks (including perhaps proprioceptive signals from the palisade endings), that are relayed through structures such as the superior colliculus and the central mesencephalic reticular formation (cMRF) to the non-twitch motoneurons. Evidence in support of this hypothesis will be discussed along with its clinical repercussions. (Grant Sponsor: This research was supported by the European Union (BIO4-CT98-0546) and DFG (SFB 462-B3)

**B12.5**

**Ocular torsional position and the use of a moving visual line to show vestibular perception**

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In this presentation the factors that affect ocular torsion position are reviewed. In particular we address the issues in using a visual line as an indicator of perceived body roll-tilt in studies of vestibular perception. In our early studies of perceived roll-tilt during centrifugation, we followed the lead of other investigators by using the visual oculogravic "illusion" to assess the extent of perceived body-roll -by asking the subject to return the visual line to the perceived earth horizontal during constant velocity off-centre rotation on a human centrifuge (or even simple en bloc roll-tilt of the body). Our experiments more recently have shown that even such a simple psychophysical task was determined by a number of factors, for example; the extent of perceived roll-tilt of the body, but also the torsional position of the eye and even whether the "target" position was earth-horizontal (SVH) or earth-vertical(SVV). Importantly horizontal angular acceleration itself induces changes in ocular torsion position and recently we have found that even the visual stimulus itself - a single short moving visual line - induces changes in ocular torsion position ("entrainment" of torsion). One principle which emerged from these studies, supported by the work of others, is that ocular torsion position is not "taken account of" by the brain so, given that other factors are controlled, a visual line falling on a torted eye will appear to be roll-tilted by about the extent of the ocular torsion.

We have shown the close correspondence between torsion position and perception 1) in patients after UVD, 2) in normals during on-centre angular acceleration where the person does not feel roll-tilted, but as the eye torts ("centered torsion") so perception closely follows 3) in experiments where we have measured ocular torsion and visual perecption during roll-tilt. Thus by excluding or controlling other factors which can influence roll-tilt perception, we have found that the simple visual task of requiring a seated patient with head erect to set a moveable visual line to the perceived earth-horizontal is a valuable clinical indicator of peripheral vestibular (and likely otolith) dysfunction. Why specifically otolith dysfunction? Because maintained otolith stimulation leads to maintained ocular torsion and patients with unilateral vestibular loss show similar maintained ocular torsion. On the other hand, maintained canal stimulation leads to eye velocity (nystagmus) but in these patients the spontaneous nystagmus is usually small or non-existent.

**B12.6**

**Non-visual ocular motor modulation of postural sway**

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In order to investigate the possible interaction of vestibulo-ocular and vestibulo-spinal functions two experiments were performed. In the first experiment (Jahn et al., Brain 2002 in press), postural sway was measured in 11 normal subjects and 10 patients suffering from vestibular neuritis while standing on foam rubber and wearing a mask that allowed fixation of a head-fixed target in darkness. While normal subjects showed no difference in sway when tested in darkness or with a head-fixed target, patients showed significantly less sway when fixating the target. The decrease in sway was accompanied by a decrease in spontaneous nystagmus. Since the fixation target was head fixed and thus offered no visual aid in stabilizing posture, this result is difficult to explain by visual mechanisms controlling postural stability. Instead, ocular motor efference copy signals may contribute to postural control.

To further test this hypothesis in a second experiment, postural sway was measured in 15 normal subjects while standing heel-to-toe under different visual conditions. As expected, a stable fixation point in otherwise darkness improved stability as compared to complete darkness. When subjects were instructed to perform smooth pursuit on a moving target, sway increased significantly in the plane and direction of target motion regardless of a stable background being present or not. This result cannot be explained by afferent visual signals about retinal slip of the visual scene alone. Thus, we conclude that eye movements per se influence postural sway. This would require direct anatomical connections between the neuronal networks for postural control and for ocular motor control. The critical ocular motor cue could be provided either by an efference copy or by a reafferent signal.

**B12.7**

**Visual vestibular mismatch in work related vestibular injury**

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Work related head injuries are often accompanied by vague complaints of dizziness, lightheadedness, imbalance, nausea and unwellness related to the injury. These symptoms often linger for a long time after the acute injury should have successfully resolved and/or been compensated for. We call this symptom set newly developed visual vestibular mismatch (VVM) and recognize it as coming from the balance system, we suspect, of the inner ear. It seems to be a specific susceptibility in some patients and not a measure of effectiveness of compensation per se. In patients who have suffered traumatic injuries, we have analyzed type of injury, time since injury, caloric results and Computerized Dynamic Posturography (CDP) results in order to try and differentiate those patients who have developed VVM from those who have not.

The autonomic correlates of vestibular pathology are becoming more understood. The effects of visual stimulation on the vestibular system are well recognized as potentially being able to elicit symptoms which are quite debilitating in some cases. Many of our patients have suffered relatively minor vestibular injuries, and their neurological examinations are often normal. However some patients can no longer tolerate jobs such as working on a chain conveyor in a sawmill, or on a moving processing line in a poultry processing factory due to the excessive movement. These patients are often rendered symptomatic by such visual stimulation, and may

sometimes be rendered dangerously unsteady. Some patients can no longer tolerate being at any height beyond the first or second rung of a stepladder. These symptoms can persist at times without abating for months and even years, preventing effective return to work despite the fact that the patient has otherwise recovered successfully from their injury.

We recognize the development of VVM as a feature of vestibular injury in some patients that may be independent of any other parameters of the injury mechanism or of the clinical abnormalities recorded. We postulate that in these patients, a subtle vestibular injury is coupled with a seemingly innate inability to tolerate even a slight difference between visual and vestibular input. This intolerance generates a chronic "motion sickness" sensation. Interestingly, this is exactly how some of our patients verbalize their symptoms. We postulate that this may reflect damage at the otolith level.

We have investigated the abnormality patterns of a group of patients referred to our work-related head injury clinic. We have correlated data in these patients with VVM and compared it to those patients who did not develop VVM after their injury. Moreover, we have correlated our results with patients referred to our clinic with non traumatic vestibular pathology, to determine whether there is a common thread to patients who have suffered VVM after a vestibular lesion, or if the common thread is just that VVM represents a subtle vestibular injury, often not detectable by caloric testing or CDP assessment in a "vestibular hypersensitive" patient.

**B12.8**

**Spatial Orientation of OKN on Earth and in Microgravity**

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When the head is tilted, spatial orientation of velocity storage orients the eye velocity axis during optokinetic nystagmus (OKN) towards the summed gravito-inertial acceleration (GIA), which in the absence of motion is the spatial vertical. During the 1998 Neurolab mission, four astronauts viewed optokinetic stimuli (OKS) during centrifugation on Earth and during space flight to determine whether adaptation to microgravity altered this spatial orientation. Subjects were exposed to centripetal accelerations of 0. 5- and 1-g directed along either the interaural axis (Gy centrifugation), or lay supine along the centrifuge arm with the centripetal acceleration directed along the body (head dorsoventral) axis (Gz centrifugation). On Earth, the centripetal acceleration summed with gravity to tilt the GIA relative to the head by 27 deg and 45 deg in the roll plane during 0. 5- and 1-g Gy centrifugation, respectively.

When undergoing Gz centrifugation the GIA was tilted by the same magnitude in the pitch plane. During orbital space flight the gravitational component was negligible, and the GIA was equivalent to the centripetal acceleration and was aligned with the interaural and dorsoventral axes during Gy and Gz centrifugation, respectively. Eye movements were measured in 3D using video. On Earth, with the centrifuge stationary, the axis of horizontal OKN was closely aligned with the OKS axis. Interaural linear accelerations of 0. 5- and 1-g during horizontal OKS generated a vertical eye movement component that tilted the axis of the OKN by 6. 4 ± 1. 5 deg and 9 ± 1. 4 deg towards the GIA, respectively. In contrast, the OKN axis remained strictly aligned with the OKS axis during vertical OKS and Gy centrifugation. During Gz centrifugation, where the GIA was aligned with the dorsoventral axis, a torsional eye movement component appeared during horizontal OKN, which tilted the OKN velocity axis 5. 5 ± 2. 3 deg in the pitch plane towards the GIA. This cross-coupling to roll was not observed during vertical OKS. The OKN response was not altered during in-flight centrifugation or after landing. Subjects also viewed OKS while statically roll-tilted on Earth before and after flight. During horizontal OKS the OKN velocity axis was tilted towards the GIA by 6. 3 ± 0. 7 deg and 9. 5 ± 1. 3 deg at 30 deg and 90 deg of static tilt, i. e. , at interaural linear accelerations of 0. 5- and 1-g, respectively. Smooth pursuit was aligned with the visual stimulus in all conditions and tilts of the GIA did not alter the direction of visual following.

These results show that eye velocity orients to the GIA through velocity storage through both pitch and roll. This orientation was maintained in-flight and did not adapt toward a body-related, vertical reference. Spatial orientation of OKN during static tilts was of the same magnitude as that during centrifugation with an equivalent interaural linear acceleration. The data also show that ocular pursuit has no orientation properties. (Supported by NAS 9-19441, NCC 9-128, ESA, and CNES. )

**B12.9**

**Encoding of Space, Calibrated and Uncalibrated, and Kinetic Parameters During Vestibular Navigation**

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Previous studies of inertially-guided navigation in humans have assessed performance without explicitly assessing strategy and those addressing strategy deployed tasks limited to a mirror reproduction of imposed movement. We used a self-rotation test in which 12 subjects performed 2 tasks; in 'go back to start' (GBS) subjects responded by moving in an opposite direction to the stimulus; in 'complete the circle' (CTC), subjects responded by literally completing the circle. Subjects sat on a motorized rotating chair in the dark with sound masking. The chair could be rotated by computer or by the subject using a chair-mounted joystick which provided a velocity demand (maximum angular velocity of 140deg/s). Subjects practiced using the joystick (without visual or auditory cues) freely and then during practice blocks of GBS and CTC. Subjects knew that the largest displacement stimuli were 360deg. For GBS and CTC, subjects were rotated with 24 different raised cosine velocity waveforms (right & left) presented in a random order of peak velocities 30, 60, 90 and 120deg/s, durations 1,2,3,4,5 and 6s and peak accelerations 16 - 377 deg/s2. Subjects were not to respond in the CTC condition if they perceived a 360deg stimulus.

Results. Grouped linear regression (n = 569) for GBS stimulus-response displacement gave R square values of 0.

75-0. 90. Group multi-regression showed that response displacement was dependent upon displacement, peak velocity and acceleration (P < 0. 0001 for all). Peak velocity was dependent upon stimulus velocity (P < 0. 0001), acceleration (P < 0. 0001) and displacement (P < 0. 05). Response acceleration was predicted by stimulus acceleration alone (P < 0. 0001). Inspection of response profiles and quantitative analysis showed differing individual strategies. Displacement performance was significantly dependent only upon kinetic parameters (stimulus peak velocity and acceleration and duration) in 3 subjects whilst in 9 it depended upon stimulus displacement with or without other kinetic parameters. Individual subjects' velocity responses could be predicted by stimulus parameters other than velocity whilst response acceleration was only ever predicted by stimulus acceleration. R squared values for CTC displacement linear regression showed 2 clusters, 0. 55-0. 9 and 0. 11-0. 04, suggesting an all-or-nothing ability. Strategy was homogenous in that all subjects used a pure displacement strategy (response profiles were rhomboid in shape with no correlation between stimulus-response kinetic parameters). We repeated GBS and CTC in 6 congenitally blind subjects and found similar responses and distribution of strategies in GBS. We again found a bi-modal CTC performance although 4 out 6 performed poorly (vs 3 out of 12 in sighted).

Comment. Subjects may perform GBS equally well by vector subtraction of displacement or purely kinetic vectors (or their combination) without the need for any spatial calibration. Tasks such as CTC require use of absolute spatial dimensions and is more akin to true spatial navigation. A bi-modal performance may be seen in novel navigation tasks in which subjects have to select an appropriate cognitive strategy. Our results also suggest separate neural representations of angular displacement, velocity and acceleration.

**B12.10**

**The study of visually-induced postural responses using virtual environments**

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The investigation of visually-induced postural responses has been a focus in our laboratory for the past decade. Previously, we have reported larger postural responses due to sinusoidal visual stimuli in subjects with vestibular disorders (Redfern and Furman, 1994), anxiety disorders (Jacob et al. , 1995), and in the elderly (Borger et al. , 1999). Furthermore, our group has explored the time-varying nature of the postural response to moving visual environments. (Loughlin et al. , 1996, Loughlin and Redfern, 2001).

Although our group has studied several novel and clinically-oriented problems related to the visual control of posture, we have been limited in our investigations by the available equipment. In some cases, we utilized a single rear-projected screen placed in front of the subject, which provided the opportunity to study several different visual scenes, but which restricted the horizontal field of view to 60o, and thus neglected important peripheral motion cues. In other instances, an Equitest posture platform was modified to present full peripheral stimulation. However, the motion of the environment was limited to pitch, and the frequency and amplitude range of the device was limited.

Motivated by these restrictions, we have developed a spatially-immersive virtual display (Medical Virtual Reality Center, MVRC) in collaboration with the Virtual Environments Group at Georgia Tech University. The main components of the MVRC include three vertical rear-projected screens that completely encompass the horizontal field of view of the subject. The addition of a front-projected screen on the floor provides approximately 110o vertical field of view. All 4 projections are controlled by commercially-available personal computers employing high-end video graphics adapters.

The use of virtual environments allows us to investigate a wide variety of problems relating to the influence of vision on postural control. The virtual environments consist of both abstract geometrical and realistic supermarket scenes. There are many psychophysical aspects of the virtual environments that can be studied, including the effects of: stereoscopic vs. monoscopic vision, head-tracked perspective correction, environment size and color, central and peripheral motion cues, spatial frequency, and movement of the user within the environment. The movement of user can occur simultaneously and independently in all six degrees-of-freedom, at frequencies ranging from 0-10 Hz and amplitudes ranging from . 001 - 50 m (0 - 360o).

Integrated into the system are several devices that allow us to explore the multisensory integration of posture. Subjects stand on a two degree-of-freedom platform that can provide both pitch and anterior-posterior translation perturbations to the somatosensory system. A treadmill will be integrated into the system that will allow the subject to drive the motion of the virtual environment. The laboratory also has the capability to induce postural responses via galvanic vestibular stimulation.

In preliminary studies, we have observed no difference in the amount of visually-induced sway elicited in patients with a prior history of vestibular nerve resection compared with controls. In addition, we have found different frequency-dependent sway patterns in children compared with adults. The use of virtual environments will allow us to explore the many different visual influences on postural control.

**B13.1**

**Visual-Vestibular and Visuovisual Interaction: From Brainstem to Cortex**

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PET and fMRI studies have revealed that excitation of the vestibular system by caloric or galvanic stimulation not only activates the parieto-insular vestibular cortex but also bilaterally deactivates the occipital visual cortex. Likewise, visual motion stimulation not only activates the visual cortex but also deactivates the parietoinsular vestibular cortex. These findings are functionally consistent with the hypothesis of an inhibitory reciprocal visual-vestibular interaction for spatial orientation and

motion perception. Transcallosal visuovisual interaction between the two hemispheres was found by using half-field visual motion stimulation: activation of motion-sensitive areas hMT/V5 and deactivations of the primary visual cortex contralateral to the stimulated hemisphere. The functional significance of these inter- and intrasensory interactions could be that they (A) allow a shift of the sensorial weight between two incongruent sensory inputs and (B) ensure a correspondence of the two hemispheres during evaluation of contradictory motion stimulation of the right and left hemifields.

In terms of mathematical modeling, these findings may reflext the concepts of a sensory conflict mechanism or a mismatch between expected and actual sensory input. Cortical activation and deactivation, as found with fMRI and PET, may correspond to a similar scheme in which activation signals more sensory input than expected, and deactivation less input than expected. Interestingly, this scheme also predicts that matching simultaneous vestibular and visual sensory input causes less activation than does sensory mismatch.

**B13.2**

**High Order Vestibular Processing: Vestibulo-Spinal and Perceptual Mechanisms**

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Munchau et al investigated the vestibularly-mediated control of head movement in spasmodic torticollis (ST), a focal dystonia involving neck muscles, with the 'head drop' technique. Subjects lie face up and with the head suspended by a sling and with attached surface neck EMG electrodes. The head is released into free-fall under two experimental instructions: 'relax and let the head drop' (passive drop or P) and 'relax but stop the head fall as soon as you can' (active drop or A). The P response is an early (ca. 25ms) EMG response which is basically preserved in ST. The A response adds a second response, normally at ca. 65ms, which is small and delayed in ST. Since separate measurements of voluntary and startle activation of neck muscles in patients is normal we conclude that there is a specific abnormal vestibulo-voluntary interaction in ST. The findings illustrate the multiple, parallel processing of vestibulo-spinal signals in man and its selective disruption by lesions at a high level in the motor system.

Seemungal et al. assessed performance and strategy during vestibular navigation in normal subjects using a self-rotation test under two different tasks: 1) 'go back to start' (GBS) in which subjects responded with movement in an opposite direction to the stimulus and 2) 'complete the circle' (CTC), subjects responded by literally completing the circle. Subjects performed uniformly well in GBS although individual strategies were varied in that, subjects could return to the origin by a pure matching of stimulus displacement or pure matching of stimulus kinetic parameters (velocity and acceleration) or sometimes by their combination. All subjects employed a displacement strategy in CTC. CTC performance across subjects was either good or very poor i. e. 'all-or-nothing' process. Our data suggest that humans may use uncalibrated displacement measures for tasks like GBS as opposed to CTC where calibrated displacement vectors are necessary.

Our results suggest that whole-body-motion trajectories may be encoded in separate neural representations of angular displacement, velocity and acceleration. In further work, Seemungal et al hypothesised that since displacement may be derived by the time integral of the vestibular signal, then an observed visual displacement, different from that expected on the basis of internal estimates of duration and velocity of motion, could affect the perception of these estimates.

This was investigated by rotating subjects over discrete angles in the dark but with vision of their angular location (defined by a large curtain surrounding subjects and decorated with images at regular angular displacements) allowed only before or at the end of a rotation. On some of the subject rotations, and during the dark, the curtain rotated by a discrete angle providing subjects with an erroneous post-displacement static visual feedback. Subjects were naïve to the curtain rotations. Subjects were asked to compare pairs of movements with a forced choice decision about which rotation was longer or faster in duration or velocity respectively.

Results showed that a static visually-derived displacement, when different from that expected from vestibular input, can not only recalibrate the perceived angular displacement but can also recalibrate the internal perception of time (ie motion duration) as well as peak acceleration, but not peak velocity. We suggest that recalibration of the internal estimate of velocity may only result from a conflict between velocity signals, and not displacement estimates.

**B13.3**

**Vestibular signals in the caudal frontal eye fields (FEF) and their role in smooth gaze movements in 3-dimensional (3-D) space**

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Vestibular-related signals are observed in multiple areas of the frontal cortex including the FEF in addition to well-known representations in parietal, somatosensory and parietoinsular cortices. The FEF is involved in control of smooth-pursuit and vergence-eye movements (e. g. McAvoy et al. 1991; Gamlin and Yoon 2000) used to track moving targets in 3-D space.

To understand the role of vestibular signals, we examined discharge characteristics of smooth-pursuit and/or vergence neurons in the caudal FEF in head-stabilized monkeys. Vergence and smooth-pursuit signals interact with the vestibular input to maintain an accurate representation of eye-movement-in-space during head movements. Moreover, to maintain the target image on the foveae during smooth gaze-tracking, both smooth-pursuit and vergence systems must use prediction. Our results suggest that vestibular signals are used not only for generating 3-D gaze-velocity signals but can also be used for prediction during smooth gaze-tracking.

A majority of smooth-pursuit neurons responded to whole body rotation in complete darkness and exhibited gaze-velocity (i. e. equal and opposite eye and head velocity sensitivities) discharge characteristics. The majority of them also discharged during vergence-tracking,

and many of them tested responded to linear acceleration during backward-forward motion of the whole body, suggesting that both semi-circular canal and otolith signals are used for their gaze-velocity responses. To further examine effects of vestibular inputs on predictive initiation of smooth-tracking, we adapted the pursuit/vergence response using trapezoidal waveform (peak velocity ~30 °/s, random inter-trial interval) pitch rotation while the monkeys tracked a spot moving in-phase with the chair. The spot had the same trajectory as the chair either in the frontal orthogonal (i. e. horizontal) plane or in depth. Before training, pitch rotation alone in total darkness did not induce horizontal or vergence eye movements. After a few days of training (1h/day), latencies of smooth-tracking with a target during pitch rotation shortened and initial eye velocities increased; average latencies of horizontal smooth-tracking shortened from 100 to 42ms, while latencies of depth-tracking shortened from 180 to less than 100ms. Latencies of horizontal-pursuit or vergence-tracking induced by identical target motion without rotation did not shorten after training. Moreover, latencies of horizontal-tracking depended clearly on the task conditions. For example, if sinusoidal spot motion was presented with phase-shifts (lead or lag) of 90° to the chair during training, latencies of the horizontal components tested by the trapezoidal trajectory of target and chair after training were 50-70ms, significantly longer than those after in-phase training. Furthermore, if the tracking target was unexpectedly stopped during chair rotation, individual eye velocity traces often revealed qualitatively distinct responses. Latencies of some pursuit neurons in the caudal FEF shortened in association with eye velocity after training.

These results suggest that vestibular signals can be used for prediction of smooth ocular tracking in our cross-axis smooth-tracking tasks and that the activity of caudal FEF neurons is involved in this prediction.

**B14.1**

**Deficits and adaptation of the translational VOR after peripheral vestibular lesions**

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The effects of unilateral labyrinthectomy on the properties of the translational vestibulo-ocular reflexes (TVORs) were investigated in rhesus monkeys trained to fixate near targets. Translational motion stimuli consisted of either steady-state lateral and fore-aft sinusoidal oscillations or short-lasting transient displacements. During small amplitude, steady-state sinusoidal lateral oscillations, a small decrease in the horizontal TVOR sensitivity and its dependence on viewing distance was observed during the first week after labyrinthectomy. These deficits gradually recovered over time. In addition, the vertical response component increased, causing a tilt of the eye velocity vector towards the lesioned side. During large, transient lateral displacements, the deficits were larger and longer lasting. Responses after labyrinthectomy were asymmetric, with eye velocity during movements towards the side of the lesion being more compromised.

The most profound effect of the lesions was observed during fore-aft motion. Whereas responses were kinematically appropriate for fixation away from the side of the lesion (e. g. , to the left after right labyrinthectomy), horizontal responses were anticompensatory during fixation at targets located ipsilateral to the side of the lesion (e. g. , for targets to the right after right labyrinthectomy). This deficit showed little recovery during the 3 month post-labyrinthectomy testing period.

The deficits after unilateral labyrinthectomy were more severe in two animals whose semicircular canals were plugged several months prior to labyrinthectomy. These differential effects suggest a functional synergy in the processing of otolith and semicircular canal signals for the generation of the VORs. In support of this notion, plugging of all semicircular canals also resulted in large changes in the otolith-ocular system. Specifically, torsional eye movements increased during lateral motion whereas vertical eye movements increased during fore-aft motion in canal-plugged animals.

These results suggest that inputs from both labyrinths, as well as strong functional canal/otolith interactions are important for the proper function of the TVORs, although the details of how bilateral signals from all vestibular sensors are processed and integrated remain unknown.

**B14.2**

**Injury-related vestibular reorganization - playground for rehabilitation**

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Afferent and commissural vestibular inputs of second order vestibular neurons in frogs are spatially very well tuned. This tuning, most likely the result of a selection process during development, becomes upset by a process of expansion of inputs that follows a vestibular nerve injury. Expansion is provoked by the inactivation of axotomized afferent nerve fibers (not by degeneration) and is limited to excitatory inputs from intact fibers. The expansion of excitatory inputs is accompanied by a reduction in the strength of inhibitory inputs whereas the synaptic inputs from axotomized afferent fibers remain unchanged. Thereby, the reduced afferent nerve activation of second order vestibular neurons is in part supplemented and the bilateral asymmetry in background excitation of central vestibular neurons is reduced. The process of expansion is graded and limited to afferent nerve inputs, as long as enough intact afferent nerve fibers exist, but involves commissural, reticular and spinal inputs, if major parts of N. VIII are inactivated. This substitution of excitatory synaptic inputs for deprived second order vestibular neurons, however, appears to occur at the expense of the spatial tuning of these neurons and their target neurons.

The convergence patterns of vestibular canal and otolith signals onto extraocular motoneurons of frogs and the vector orientations for the activation of maximal responses are precisely known. Such detailed information provides a platform for the analysis of the spatial tuning characteristics of motor responses in chronic RA frogs (i. e. two months after a section of the ramus anterior of N. VIII). The vector orientations of canal- as well as of macula-related responses of the abducens nerve on the intact side were distinctly altered. Macular responses of the abducens

nerve originate in the contralateral utricle in controls. In chronic RA frogs, however, utricular afferent inputs from the intact side activate the responses of the abducens nerves on either side. In addition, the abducens nerve on the intact side receives an input component from the vertical otolith that was not seen on the operated side nor in controls.

Very similar postlesional reorganizational changes are known for other sensory modalities in mammals and undesired functional consequences are known in man as well (e. g. phantom sensations or even pain months after arm amputation). Thus, expansion of excitatory synaptic inputs may be expected in patients after vestibular neuritis or after a loss of labyrinthine function as well. Since postlesional synaptic plasticity is an activity-dependent process, the selection of new synaptic inputs during the period of reorganization can be influenced by the behavioral activities of the patient during this period. Consistent with results of rehabilitative therapy we expect that physically active patients develop functionally more beneficial new connections than patients who stay at rest. In the former group context specific sensory feedback activity will shape the changing response properties whereas in the latter group reorganization will occur more at random.

**B14.3**

**Neuronal and synaptic adaptations in vestibular nucleus neurons after labyrinthectomy - the foundation for compensation?**

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Recent studies have shown that in the initial stages of vestibular compensation after unilateral labyrinthectomy (UL), significant changes occur in the intrinsic properties of ipsi-lesional medial vestibular nucleus (MVN) neurons, and in their responsiveness to GABA and glycine. These changes are in the appropriate direction to promote the recovery of their resting discharge after de-afferentation. Thus there is an increase in the intrinsic excitability of rostral "Type B" MVN cells within 4h post-UL, mediated by changes in expression or function of ion channels including Ca channels that are active around their resting membrane potential. There is also a rapid down-regulation of the functional efficacy of GABA-A and GABA-B receptors within 4h post-UL; while the efficacy of GABA-A receptors recovers after a few days, GABA-B receptors remain down-regulated. Interestingly, ipsi-lesional flocculectomy at the time of UL prevents the post-lesional increase in intrinsic excitability in ipsi-lesional MVN neurons, but does not prevent the down-regulation of GABA receptor efficacy. Micro-injections into the ips-lesional flocculus of drugs that inhibit LTD in cerebellar cortex, also prevent the increase in intrinsic excitability of ipsi-lesional MVN neurons. These findings indicate that adaptive changes in the properties of MVN neurons after de-afferentation may be an important mechanism that promotes the recovery of resting discharge in these cells during vestibular compensation, and implicate the cerebellar flocculus in this early recovery.

**B14.4**

**Trophic Factor-Induced Recovery of Mammalian VOR**

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Hair cells in the vestibular neuroepithelia transduce linear and angular acceleration information and induce neurotransmission that contributes to vestibulo-ocular reflexes (VOR). Loss of hair cells and their neural connections leads to permanent peripheral vestibular dysfunction, which can be compensated to varying degrees through central mechanisms. In addition, recent data suggest that the mammalian vestibular neuroepithelium has some inherent potential for recovery of neuroepithelial integrity after an injury such as is caused by aminoglycoside antibiotics.

We describe a different degree of VOR recovery in gentamicin-lesioned guinea pigs treated with either brain derived neurotrophic factor (BDNF) or one of two other trophic factor combinations infused into the inner ear one week after bilateral topical gentamicin exposure. Measures of horizontal semicircular canal function [horizontal vestibulo-ocular reflex (hVOR) gain and phase] were apparently modulated by the trophic factor treatment achieving a full recovery of hVOR gain not seen in animals ablated with gentamicin and not treated with trophic factor. Measures of macular function were also tested using off earth vertical axis constant velocity rotation. Maculo-ocular reflex gain and modulation bias recovered fully in animals treated with BDNF or trophic factor mixtures containing BDNF. For the maculo-ocular reflex measures the recovery effect was most marked when the animal was rotated in the direction of the trophic factor treated ear.

These data suggest that BDNF was more important for the recovery of maculo-ocular reflexes than for semicircular canal function. These data lend further support to the notion that the mammalian vestibular periphery has some potential for recovery following a toxic injury that can be enhanced by altering the inner ear microenvironment.

**B14.5**

**Changes in Angular Vestibuloocular Reflexes Following Unilateral Lesions of the Labyrinth**

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The exquisite accuracy of the horizontal angular VOR is dependent upon inputs from both labyrinths. Unilateral vestibular lesions such as labyrinthectomy, plugging of the semicircular canals, or intratympanic gentamicin lead to asymmetries in vestibuloocular responses. These asymmetries are particularly prominent for rotational stimuli that are of higher frequency and acceleration. For the horizontal VOR, the response to rotations that are inhibitory with respect to the horizontal canal on the intact side is diminished in comparison to the VOR elicited by rotations that are excitatory for this canal.

Our investigations in the squirrel monkey of the horizontal VOR evoked by sinusoidal rotations (0. 5 - 15 Hz, peak velocity 20 – 150 deg/s) and by steps of acceleration (500 – 3000 deg/s$^2$) provide insight into the physiological basis of these asymmetries. Analysis of the

reflex in animals with intact vestibular function reveals two components of the responses. The linear component has a constant gain for this range of stimuli and provides a signal proportional to angular head velocity. The nonlinear (phasic) component has a gain that rises with velocity at frequencies >2 Hz and shows rectification in that it is rapidly driven into inhibitory cutoff.

We developed a mathematical model of the VOR with inputs from pathways representing these linear and nonlinear components to simulate the reflex in normal animals. Changes in the central gain on the intact side for each of these pathways (without changes in dynamics) accounted for the changes in the VOR following unilateral vestibular lesions. Asymmetries can be understood based upon the nonlinear component being more highly modifiable than the linear component. This nonlinear component arising from vestibular inputs on the intact side can restore relatively normal gain for contralesional rotations following a unilateral lesion. The nonlinear component on the intact side makes relatively little contribution to the response for ipsilesional rotations because it is rapidly driven into inhibitory cutoff.

While the asymmetries in the horizontal angular VOR noted initially after the lesion are comparable for unilateral labyrinthectomy and for unilateral plugging of the three semicircular canals in the squirrel monkey, recovery of gain for responses to ipsilesional rotations is noted long-term after canal plugging but not after labyrinthectomy. The recovery after plugging may be due to the preserved resting discharge rate in vestibular-nerve afferents on the side of the plug.

The findings have implications for understanding asymmetries in the VOR after intratympanic injection of gentamicin in patients with intractable vertigo due to unilateral Meniere's disease. The gain attributable to excitation of semicircular canals on the treated side is greater than that after unilateral surgical ablation of vestibular function. Long-term recovery of function is noted in some cases after intratympanic gentamicin. Single-unit recordings from vestibular-nerve afferents in chinchillas after similar treatment with gentamicin injected into the middle ear reveal preservation of resting activity but marked reduction in the sensitivity of these afferents to motion stimuli. Thus, resting activity in afferents may have an important role in restoration of symmetry.

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**B14.6**

**The vestibular system is necessary for hippocampal function**

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We have conducted behavioural, electrophysiological and neurochemical studies to investigate the effects of unilateral and bilateral vestibular deafferentation (UVD and BVD, respectively) on the hippocampus. Our behavioural studies have shown that BVD results in spatial learning deficits in rats which could not be readily attributed to changes in motor control, at least 5 weeks following BVD. We have shown that electrical stimulation of the vestibular nucleus systematically evokes responses in single hippocampal neurons with a polysynaptic latency. BVD, at least 60 days before recording, resulted in dramatic changes in the firing of hippocampal place cells, including an increased baseline discharge and poorly defined place fields with greater instability. In the same animals, EEG activity was also severely disrupted.

Our in vitro electrophysiological studies have shown that UVD results in dramatic decreases in ipsilateral hippocampal potentials in hippocampal slices removed from chronically compensated animals. In neurochemical studies, we have found that UVD results in long-term changes in both neuronal nitric oxide synthase (nNOS) expression in the ipsilateral dentate gryus and a decrease in the expression of the NR1 and NR2A N-methyl-D-aspartate (NMDA) receptor subunit expression in the ipsilateral CA2/3 region.

Taken together, these results suggest that vestibular information is important for the spatial representations constructed by the hippocampus and that vestibular lesions are likely to disrupt forms of plasticity such as long-term potentiation and long-term depression. .

**B15.1**

**High Concenration Intratympanic Gentamicin Injection Technique in Intractable Meniere's Disease**

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Intratympanic gentamicin therapy is one of the few new frontiers in treatment of Meniere's disease and may replace vestibular surgery. Many papers have reported high success rates in treating episodic vertigo of Meniere's disease, but technique, dose, duration, and treatment philosophy varied considerably. But hearing loss was typically reported in about 30% of patients. The purpose of this paper is to describe the efficacy of a low dose, high concentration, long interval technique for gentamicin therapy.

Method. Four patients who were diagnosed with intractable Meniere's disease, based on the 1995 guidelines of the American Academy of Otolaryngology Head and Neck Surgery, were selected. Each patient received a ventilation tube on the lesion side, and then gentamicin was infused as 0. 3cc of an 80mg/ml solution at weekly interval for a total of 3 times by 25 gauge spinal needle. The ending time is determined by a new vertigo attack or decreasing gain on SHA testing. All patients were evaluated by questionnaire and pure tone audiometer(included 8000-12000Hz).

Result. In two patients, all three injections were required. For 24 month follow up period, vertigo was controlled well in all patients and hearing level was improved in two patients.

Conclusion. The high concentration gentamicin injection method is a simple and effective method to treat intractable Meniere's disease.

**B15.2**

**Daily Brandt-Daroff Exercises Reduce Recurrence of**

**Benign Paroxysmal Positional Vertigo**

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Benign Paroxsymal Positional Vertigo (BPPV) is treated effectively with the canalith repositioning procedure (Epley,1992), the average success rate being 76% (Harvey, Hain, & Adamic, 1994). Of patients treated successfully with the procedure, 44% redevelop BPPV within 2 to 4 years (Hain, Helminski, Reis, & Uddin, 2000; Girardi & Konrad,1997). A preliminary investigation suggested that performing daily Brandt-Daroff exercises (Brandt & Daroff, 1980) increases the time to and decreases the rate of recurrence of BPPV (Amin, Girardi, Neill, Hughes, & Konrad, 1999). However, reliable inferences cannot be made from this study due to the small number of subjects. The purpose of this investigation was to determine if following successful treatment of BPPV, a daily routine of Brandt013Daroff exercises will increase the time to recurrence and reduce the rate of recurrence of BPPV.

We identified 112 subjects with BPPV involving the posterior semicircular canal, treated successfully with the canalith repositioning procedure. There were two groups of patients 013 83 patients in group 1 were not treated and 29 patients in group 2 were treated with ongoing exercises. The treatment group performed 2 cycles of the Brandt-Daroff exercises daily. Subjects were followed and if dizziness recurred, the subject was reevaluated clinically.

Of the 112 subjects, symptoms recurred overall in 36% (n = 40), in 43% of the no treatment group (n = 26/83) and in 24% of the treatment group (n = 7/29). The difference in frequency between the 2 groups was significant (Pearson 0632, P=0. 067). There was no significant difference in the time to recurrence between the 2 groups (P = 0. 680).

We also examined whether history of recurrent BPPV significantly affected the frequency of recurrence of BPPV between the no-treatment and treatment groups. Of the 112 subjects, 106 subjects were analyzed. BPPV recurred in 13% (n=2/15) of the treatment group with no history of recurrence, 36% (n=5/14) of the treatment group with a history of recurrence, 35% (n=17/31) of the no-treatment group with no history, and 55% (n=16/29) of the no-treatment group with a history. The differences (Pearson 0632, P= 0. 053) and observed trend (P = 0. 009) were significant between the groups. There was no difference in the time to recurrence between the groups (P = 0. 229).

Our results suggest that a daily routine of Brandt-Daroff exercises reduces the frequency of recurrence of BPPV but does not affect the time to recurrence of BPPV. A history of recurrent BPPV is associated with an increase in rate of recurrence of BPPV. (Supported by National Institute of Health, National Institute on Aging, 1 R15 AG17567-01A1)

**B15.3**

**Proteomic Analysis of the Inner Ear : Identification of the Cochlin Isoforms and Their Importance in the Pathophysiology DFNA9-Induced Meniere's Disease**

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In recent years, due to the technological advances of molecular biology, there have been many advances in our understanding of hereditary hearing impairment (HHI). Some of the HHI genes are cloned and the mutations of those genes are identified. Much knowledge has accumulated about the HHI genes; however, little research has been done regarding the protein products of those genes.

In order to characterize deafness genes at the protein level as well as other inner ear proteins, we performed a proteomic analysis of the inner ear proteins using two-dimensional gel electrophoresis.

In the process of analysis, we found very unique properties of the protein product of a deafness gene, COCH . The COCH gene is responsible for one of the HHI, DFNB12. The primary pathologic change of the DFNA9 is a deposit of acid polymucosaccharide ground substance in the cribrous areas, in the spiral ligament, limbus, and spiral lamina of the cochlea, and in the stroma of the maculae and cristae. The end result is neuronal degeneration in the sense organs.

DFNA9 is the locus in humans reported to be involved in vestibular problems as part of the non-syndromic deafness phenotype. It is suggested that the COCH gene may be one of the genetic factors contributing to Meniere's disease and the possibility of a COCH mutation should be considered in patients with Meniere's disease symptoms.

The results of the proteomic analysis of bovine inner ear proteins revealed that the Coch protein (Cochlin) constitutes 70% of inner ear proteins and is composed of 16 different protein spots, with heterogeneity in charge and size. These spots are classified into 3 groups of isoform, p63s, p44s and p40s. Heterogeneity of this protein suggests that the Coch gene is processed in several ways, at the transcriptional and/or posttranslational level. And very interestingly, all of the reported mutation sites of COCH gene are found only in p63 isofrom and not in others.

Proteomics is a powerful tool to understand the inner ear diseases.

**B15.4**

**A model experiment of BPPV mechanism using the whole membranous labyrinth**

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Etiology of benign paroxysmal positional vertigo (BPPV) is still controversial; however, canalolithiasis and cupulolithiasis have been regarded as the possible candidates. We had demonstrated in a previous study using the isolated frog posterior semicircular canal (psc) that canalolithiasis would be the most valid mechanism of BPPV. In this study, the whole membranous labyrinth was used in order to replicate the human vestibule.

Method. The psc of bull frogs were exposed leaving the remaining membranous labyrinth encapsulated in the otic capsule. Vibration was applied to the surface of the bony capsule using a conventional surgical drill in order to

dislodge the otoconia from the utricle. The inferior vestibular nerve was sucked into a glass suction electrode to record compound action potentials (CAP). In the first experiment (Experiment 1a), the otoconia were placed on the copular surface to mimic the condition of cupulolithiasis. In the second experiment (Experiment 2a), the otoconia were inserted into the psc lumen to mimic the condition of canalolithiasis.

Next, we conducted the same experiment by an easier method. A part of membranous labyrinth was cut to create a tiny opening. Small piece of otoconia was introduced through this opening into the canal lumen to mimic a condition of Experiment 1a and 2a. These are Experiment 1b and 2b.

Results. 1. Experiment 1 (model of cupulolithiasis) When the otoconia were placed on the copular surface, the CAP instantaneously changed according to the gravity produced by the otoconia. In Experiment 1a, the average and standard deviation of the latency was 1.8±0. 2s. The discharge was long sustained. The average of the response duration was more than 10 minutes. In Experiment 1b, the average and standard deviation of the latency was 1.8±0. 3s. The average of response duration was more than 10 minutes.

2. Experiment 2 (model of canalolithiasis) When the otoconia moved in the canal, the CAP changed after a latent period. In Experiment 2a, the average of the latency was 3.5±0.4s, which was longer than that of Experiment 1. The average of the response duration was 11. 7±1.2s, which was shorter than that of Experiment 1. In Experiment 2b, the average of the latency was 4. 0±0. 7s. The average of the response duration was 17.3±3.8s.

Conclusion. The results that the response duration was shorter and the latency was longer in canalolithiasis are compatible with those of the previous study using the isolated canal. Canalolithiasis is the most likely mechanism of BPPV which usually shows nystagmus with short duration and long latency.

**B15.5**

**Possible role of TNF-a and p55 and p75 receptors in inner ear diseases, especially in Meniere's disease**

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Damage of the cochlea causes up-regulation of TNF-a and their receptors P55 and P75. Recently, hearing loss (HL) in autoimmune inner ear disease and in Ménière's disease could be prevented by administrating recombinant human TNF-a receptor P75 monomer fused with the Fc domain of human IgG1 (ethanecerpt, Embrel®). We studied in an animal model up-regulation of TNF-a, its receptors and the efficacy of anti-TNF-a monoclonal antibody (infliximab, Ramicade®) in preventing HL in this animal model, and the efficacy of infliximab in five patients with advanced Ménière's disease.

Methods. 35 pigmented guinea pigs, were used in the study; 3 for immunohistochemistry normal control group, 20 for vibration non-treatment group, 12 were pre-treated with inflIximab (5 animals received i. v. injection, 8 received round window membrane delivery). After exposing guinea pig to vibration (15 min, 250 Hz, 8. 7 m/s2) hearing was measured and recovery followed for 24 hours. Monoclonal anti-human TNF-a RI and TNF-a RII antibodies, and Monoclonal anti-human TNF-a antibody were used to detect the expression of TNF-a and it's receptors in cochlea. In five patients with severe Meniere's disease a three months trial with infliximab was attempted.

Results. In guinea pigs the average HL was 42 dB after exposure to vibration. Severe outer hair cell loss and spot wise inner hair cell loss were noticed. Wide scar formation was found mainly in the outer hair cells and some inner hair cells. Strong co-expression of TNF-a, p55 (TNF RI) and p75 (TNF RII) receptors was demonstrated in the outer hair cells, inner hair cells, stria vascularis and in the spiral ganglion cells. In the 12 treated animals, the average HL was 78 dB in i. v. group and 41 dB in round window membrane delivery group showing no protection against vibration trauma. In the five patients treated with combination of infliximab, cortisone and azatioprin neither hearing nor vestibular symptoms were alleviated by the treatment. One subject ceased prematurely the treatment due to adverse effects.

Conclusions. In the animal model, trauma up-regulates the expression of TNF-a, p55 and p75 receptors in the cochlea, which maybe responsible for the hair cell loss and cochlear neuron damage. Efforts to prevent damage with TNF-a blocking agent infliximab was neither successful in animals nor in patients with severe Ménière's disease did not alleviate the hearing loss and vestibular symptoms in contrast to ethanecerpt.

**B15.6**

**Static direction-changing horizontal positional nystagmus of the peripheral origin**

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Positional nystagmus can be classified into two categories. One is paroxysmal and the other is static. BPPV is a typical paroxysmal positional nystagmus caused by a peripheral lesion. On the other hand, direction-changing horizontal positional nystagmus is a marked static positional nystagmus. Static positional nystagmus persists as long as the critical position of the head is maintained and generally causes less vertiginous sensation and no fatigability. From the characteristic direction of horizontal nystagmus in the head right position and in the head left position we often divide static direction-changing horizontal positional nystagmus (SDCHPN) into geotropic and apogeotropic groups. Recent evidence indicates that SDCHPN is mostly caused by a peripheral lesion. Concerning the mechanism of SDCHPN of the peripheral origin, the cupulolithiasis theory and buoyancy theory have been advanced. In this study the clinical features and nystagmus appearance of SDCHPN of the peripheral origin were examined.

Eleven apogeotropic SDCHPN and 16 geotropic SDCHPN were selected, based on full clinical observations and further positional examinations. Ordinary vestibular tests (gaze nystagmus, positionl nystagmus, saccade, slow pursuit, optokinetic nystagmus, ocular fixation suppression, caloric nystagmus) were carried out. Additional positional nystagmus tests in every head position with a difference of

30 degrees around the sitting position were performed. Gd enhanced MRI or enhanced CT showed almost normal findings.

Both apogeotropic SDCHPN and geotropic SDCHPN had quite similar characteristics except for the direction of nystagmus. And apogeotropic SDCHPN had a nystagmus appearance similar to the horizontal canal BPPV (cupulolithiasis type). However SDCHPN never changed to other forms of positional nystagmus such as horizontal canal BPPV (canalolithiasis type) or to other forms of SDCHPN. The results indicate that the cupulolithiasis theory and/or the canalolithiasis theory are insufficient to explain SDCHPN.

Furthermore, in both apogeotropic SDCHPN and geotropic SDCHPN, there were head positions at which the direction of SDCHPN reversed. These critical head positions were situated on the vertical plane turning about 30-degrees from the sagittal plane. The slow phase velocity of SDCHPN was changed on the basis of this vertical plane. SDCHPN never disappeared in the 30-degree head bending forward position where the horizontal semicircular canal is situated horizontally.

These findings suggest that the buoyancy theory on the endolymph in the horizontal semicircular canal is not applicable to SDCHPN. A density change of the cupula in the unilateral horizontal semicircular canal is the most likely origin of SDCHPN: a heavy cupula or a light cupula. A heavy cupula always deviates to the ground, producing apogeotropic SDCHPN and a light cupula always deviates from the ground, producing geotropic SDCHPN. The critical head position on the vertical plane could be a head position in which the cupula with its density changed is always neutral against gravity. The lesional side is speculated to be the side on which the direction of SDCHPN is reversed in the supine position. However, it remains unknown what makes the cupula become heavy or light.

**B15.7**

**Glycerol VEMP**

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In order to diagnose the endolymphatic hydrops (EH) of the inner ear, the Glycerol (G) test, electrocochleography (ECochG) and the Furosemide VOR (FVOR) test have been used. Both the G test and ECochG are usually useless in patients with normal hearing and total deafness. Neither is the FVOR test good enough to evaluate the affected ear. Because VEMP is a saccule-origin response and is independent of hearing acuity, we have attempted to utilize the VEMP with diuretics (Glycerol). In this study, VEMP was done before and during the G test (Glycerol VEMP).

Method. VEMP was repeated immediately before, 1 hour and 2 hours after the intravenous administration of 500ml of 10% Glycerol. Because the p13-n23 amplitude of the VEMP based on the unrectified EMG is correlated to the muscle activity of the SCM muscle during the test, we measured the muscle activity of the SCM muscle by the background integrated EMG, an area under the averaged rectified EMG from -20msec to 0msec before the sound stimulation. The correction of the p13-n23 amplitude was calculated on the basis of the following; corrected amplitude = p13-n23 amplitude of the averaged unrectified EMG / background integrated EMG. When the p13-n23 amplitude changed abnormally, the test was diagnosed as positive. Fifty-five patients suffering from the peripheral vestibular disease including unilateral Meniere's disease (MD), delayed endolymphatic hydrops (DEH) and sudden deafness (SD) were tested.

Result. Eleven of 21 patients (52%) with the unilateral MD and six of ten (60%) with the DEH were positive in the Glycerol VEMP. In the SD, only one-fourth of the patients (two out of eight) were positive. In the EH disease, such as the MD and DEH, Glycerol VEMP resulted in a higher positive rate compared in the non-EH disease. In addition, even more patients (62%) with the unilateral MD were judged to be abnormal when results of the Glycerol VEMP were combined with those of the G test, ECochG or FVOR test.

Conclusion. Glycerol VEMP is a useful EH test, and that a test battery of the Glycerol VEMP with one of other three tests, such as the G test, ECochG and FVOR test, are helpful in diagnosing the EH of the inner ear.

**B15.8**

**3D Vector Analysis Of Benign Paroxysmal Positional Vertigo And Variants**

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Benign paroxysmal positional vertigo (BPPV) is a common cause of vertigo. The pathophysiology of the classic BPPV is that of dislodged, free-floating otoconia (calcium carbonate crystals) from the utricular macula that are misplaced in the posterior semicircular canal, also referred to as canalithiasis. Different variants of BPPV have been described, which may involve free otoconia in the lateral or anterior semicircular canal; or clumped otoconia adherent to the hair cells, i. e. cupulolithiasis.

The aim of this investigation was to determine if three-dimensional vector analysis of the positional nystagmus provoked by repositioning the patient's head predicts the semicircular canals involved in BPPV. Positional nystamus from patients clinically diagnosed with BPPV or variants was recorded using the three-dimensional search coil technique in a two-axis whole-body rotator, which permit repositioning the patient's head in order to provoke the nystagmus. These patients had previously undergone Epley's or Semont's particle repositioning manoeuvres without successful resolution of their positional vertigo.

Three-dimensional vector analysis of the slow phase component of their positional nystagmus was performed and compared with published anatomical orientations of the semicircular canals. In the classic BPPV i. e. canalithiasis of the posterior canal, the eye velocity vector of the positional nsytagmus aligned with the on-direction of the affected posterior canal. In instances where the eye velocity vector did not align well with the on-direction of a single semicircular canal, we deduced that canalithiasis was present in more than one canal. In the lateral canal cupulolithiasis variant, the eye velocity vector of the positional nystagmus was aligned with the on-direction of the contralateral lateral canal instead of the ipsilateral lateral canal of the dependent ear.

Based on the evidence from the vector analysis of

their positional nystagmus, the appropriate canalith repositioning manoeuvre was performed. The majority of the patients treated in this way had complete resolution of their symptoms. Vector analysis of the positional nystagmus at the time of the canalith repositioning manouevre is a useful tool in the diagnosis and treatment of BPPV.

**B16.1**

**Two New Tools and Tests to Measure Ocular and Vestibular Anomalies of Craniofacial Asymmetries**

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Craniofacial asymmetries in vestibular organ anatomy (CFA) are now well identified as a new syndrome whose objective signs are ocular exocyclotorsion, modification of the counterrolling reflex (OCR), congenital interlabyrinthine dysfunction, muscular dystony in charge of head tilt and scoliotic attitude. These anomalies induce deformation of the body schema. ( Rousie et al. 1999). Two tests and tools have been employed to measure these anomalies:

The VEONIS system and the impulsional rotational test( IRT)[4]. This protocol was preferred to the traditional caloric test whose results were not correlated with the symptoms constantly described by the subjects.

The scanning laser ophthalmoscope (SLO) allowing a precise comparison R. /L. of the foveal position (d°) of the eye in the frontal plane in a referred position of the head: SLO gives the ocular position of the eye acquired by the OCR and especially the exact position of the foveas before testing the OCR. This last point is seldom taken into account in studies of OCR and we wanted to check its incidence.

We carried out IRT and SLO tests on 50 CFA subjects. The IRT protocol tested the per and post rotational responses (frequency and velocity of slow phase, quick phase of nystagmus). Concerning the SLO: the measurement of ocular foveal locations were made in position of head referred using a special device and an electronic clinometer*. The OCR was tested with small tilts 3°,6°,15° considered as more physiological than those usually used (15°, 30°, 45°) IRT, because of its high sensitivity and its mode of physiological stimulation highlighted functional interlabyrinthine asymmetries corresponding to the evoked symptoms (dizziness, off-balance, walking deviation) for 47/50 subjects. SLO highlighted, in gravitational right head position, a high frequency of ocular torsion (3°to15° for 44/50 subjects) and especially the presence of a threshold in the amplitude of stimulation of the OCR on the torsional eye. The OCR appeared only to 15° of head tilt

The first interest of this study carried out on CFA subjects presenting a functional symptomatology was to highlight the objective anomalies in agreement with their subjective symptoms using two new tools and small amplitudes of stimulation . The second interest was to underline that strong neurosensorial stimulations erase 'normal' physiological responses. These results suggest that strong stimulations as caloric tests and head tilts superior to 15° induce different responses from those elaborated in the everyday life by the CFA subjects but nevertheless responsible of anomalies . This observations requires complementary studies to identify the neural basis of such responses.

**B16.2**

**Experimental study on hydrodynamics of caloric response**

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The mechanism of the caloric response is still controversial. Thermoconvective flow is credited to be the most relevant mechanism. However, there are reports that the caloric response was still present even under microgravity or after canal plugging.

To clarify the role of thermoconvective flow and volume change of the endolymph in the caloric response, the frog posterior semicircular canals (PSC) were used. The PSC were placed in the horizontal or the vertical plane in frog Ringer's solution. The PSC was sutured by 10 nylon for a model of canal plugging. The ampullary nerve was sucked into a glass suction electrode to record action potentials evoked by a cooling stimulus. The number of spikes and the duration of action potentials in the vertical plane were greater than in the horizontal plane. This is probably because both thermoconvective flow and volume change are effective in the vertical plane, whereas only volume change is effective in the horizontal plane. When the sutured PSC were cooled, the volume change increased compared to the unsutured PSC. In this case, the thermoconvective flow was completely eliminated.

The above findings indicate that the thermoconvective flow of the endolymph plays a major role of caloric response and the canal plugging increases the effect of volume change.

**B16.3**

**Contribution of torsional eye movement measurement in daily practice**

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When just looking at the eye through Frenzel glasses or with a Video-Nystagmo-Scope (VNS), the direction of the jerks of torsional nystagmus is easily detected in the event of canalolithiasis of the posterior canal. On the other hand during the counter-rolling test, the size of the angle of the eye torsion, about 4° in response to a 45° head tilt, and the absence of steady anatomical reference close to iris, prevents any reliable clinical appreciation.

Imagined by Philippe Guillemant, the application of a mathematical neural network on the iris image coming from a VNS camera allows quasi-immediate availability of the device, without any difficult setup. The reliability of measurements is observable in real time thanks to the superposition of a synthetic reference mark on the iris image, making it possible to check the reality of the tracking.

Using this method we already have the possibility to analyze the torsional component of any nystagmus occurring during a standard vestibular examination : spontaneous, positional, induced by head movements, induced by caloric stimulation, or even vibration induced nystagmus. But we also have the opportunity to check the counter-roll angle, and therefore have an access to the otolithic vestibular response to steady head positions referred to gravity vector. Here, we will first describe torsional nystagmus, whatever the origin, then we will discuss static counter-roll eye torsion in response to head tilt test : protocol and normal results.

**B16.4**

**Ocularcounterrolling in a population of patients suffering from acoustic neuromas**

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Ocular Counterrolling is the approximately conjugate rotational movements of the eyes about their visual axis (naso-occipital axis, X-axis) opposite to the direction of head tilt

The 3-dimensional eye movement responses to a standard 45° passive lateral (about the X-axis) head tilt on the patient's shoulder were recorded by an infra-red oculographic system (SYNAPSIS). Each eye was measured separately. According to the fact that the gain of the otolith-ocular reflex is critically dependent upon context and is proportional to target proximity, the patients were requested to fixate a visual target at a distance of 2 m. The paradigm was as follows : passive 45° right head tilt, position maintained 30 sec then passive 45° left head tilt and position re-maintained for 30 sec.

The OCR ranged from 4° to 8° in a population of normal healthy volunteers. 20 patients who underwent vestibular sections secondary to excision of acoustic neuromas (by trans labyrinthine approach) demonstrated characteristics profiles of OCR which, when compared to normal healthy volunteers were asymmetric. The OCR abnormalities were evident when the patient was tilted to the intact side and appeared normal when tilted to the lesioned side. This asymmetry was obvious when the eye ipsilateral to the lesioned side was recorded.

These abnormalities were dependent on the delay after surgery and on the size of the acoustic neuroma.

**B16.5**

**Delayed vestibular evoked myogenic potentials in radiation-induced otitis media**

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Objectives. Radiation-induced otitis media (ROM) is termed as a chronic inflammation in the middle ear after irradiation on the head and neck region. The purpose of this study is to apply VEMP test in cases of ROM and chronic otitis media (COM), in order to elucidate whether ROM is different from COM.

Patients. Fourteen nasopharyngeal carcinoma (NPC) patients of ROM (18 ears) and another 14 age-, and sex-matched patients of conventional COM (18 ears) were subjected to VEMP test. Each ear was stimulated by a short-tone burst (95 dB, 500 Hz), followed by tapping on the forehead with a tendon hammer, 200 times with a frequency of 5Hz, as the same in the tone-burst stimulation.

Results. In ROM group, delayed VEMPs were detected in 11 ears, absent VEMPs in one ear, and normal VEMPs in 6 ears (33%). In comparison with those of COM group, delayed VEMPs in 2 ears, absent VEMPs in 6 ears, and normal VEMPs in 10 ears (56%), exhibits a non-significant difference in the appearance of normal VEMPs ($p>0.05$). However, by applying tapping method, the normal rate for VEMPs in COM group increases up to 89%, compared to 33% in ROM group with a significant difference ($p<0.05$). For those with delayed VEMPs in ROM or COM group, the results remained unchanged by tapping method.

Conclusions. ROM should be considered as a different disease entity from the conventional COM. The former affects more extended and results in delayed VEMPs, which is attributed to a retro-labyrinthine involvement.

**B16.6**

**Neurotoxic effects of hair curling solution on vestibulo-ocular reflex system of guinea pigs**

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Objective. Potassium bromate (KBrO3) and thioglycolate (TG) are two components of hair curling solution. The neurotoxic effects of KBrO3 and TG on vestibulo-ocular reflex (VOR) system have not been elucidated.

Methods. VOR system was evaluated by caloric test coupled with ENG recordings after subcutaneous injection of KBrO3 (20 mg/Kg or 50mg/Kg) or TG (15mg/Kg) in guinea pigs, either alone or in combination once daily for 14 consecutive days. Motor equilibrium performance and spontaneous locomotor activity of guinea pigs were conducted. After physiological testings, the animals were sacrificed for enzyme assay of the cerebellum, bromide measurement,and histopathological study.

Results. KBrO3 produced abnormal caloric responses in a concentration-dependent manner and TG enhanced this abnormality. Our clinical patients, ten female hairdressers exposed to the hair curling solution for 10-30 years revealed a similar dysfunction in the caloric test. The possible mechanism of this adverse effect was studied: the cerebellar regulated functions such as motor equilibrium performance and spontaneous locomotor activity of guinea pigs were reduced; the enzymatic Na+/K+-ATPase and Ca2+-ATPase activities of cerebellar tissues were significantly decreased; and the loss of Purkinje cells as well as the derangement of granular cell layer of the cerebellar cortex was revealed after treatment with KBrO3 plus TG.

Conclusions. KBrO3 plus TG is toxic to VOR system, mediated by, at least in part, the dysfunction of higher cerebellar regulatory mechanism.

**B17.1**
**Ototoxicity and the horizontal VOR**
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We studied the dynamics of the horizontal vestibulo-ocular reflex (VOR) in 35 patients with documented gentamicin ototoxicity using sine and step rotational stimuli. All patients complained of imbalance and 32 of 35 reported oscillopsia. Twenty-one were tested with the bedside head-thrust test and all were abnormal (compensatory saccades in both directions). Eye movements were recorded with EOG and patients were rotated in the dark at multiple frequencies and accelerations.

The main findings were: 1) shortening of the VOR dominant time constant (<5 seconds in all cases and in many <0. 5 seconds); 2) acceleration saturation (little or no response to accelerations > 1000° / $sec^2$). Because of the shortened time constants, all patients had low gain at low frequencies and low accelerations (e. g. , mean ±1 s. d. , 0. 08 ± 0. 07 at 0. 05 Hz, peak acceleration 74°/$sec^2$). Some had relatively preserved gain at higher frequencies and accelerations (e. g. , gain of 0. 44 ± 0. 25 at 0. 8 Hz, peak acceleration 285°/$sec^2$) despite having minimal response to high acceleration steps.

The dramatic acceleration saturation seen in these patients with gentamicin ototoxicity likely results from severe loss of hair cells, particularly type 1 hair cells at the crest of the cristae. The most sensitive test to identify vestibular ototoxicity are tests that use high accelerations (the bedside head-thrust test or high acceleration step changes in velocity). Sinusoidal tests at intermediate frequencies and low accelerations (0. 5 to 1. 5 Hz, peak acceleration <300°/$sec^2$) can be relatively maintained, particularly in milder cases.

**B17.2**
**Vestibular Evoked Potentials to Acceleration Impulses**
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The method of induction and recording of Vestibular Evoked Potentials (VEPs) to acceleration impulses which has been developed at the Hadassah-Hebrew University Medical Center, Jerusalem, will be presented. This method was used for investigations in experimental animals and later was implemented in human beings. It is based on the presentation of short intense acceleration impulses with rise time of 1-3 msec and intensity, which can be varied between 1000- and 20,000°/S2. The transfer of angular acceleration impulses to the subject's head is achieved by two special metal drums. The stimuli can be delivered at various rates (0. 5-2/S is usually being used). The recorded VsEPs is extracted by evoked response system at 3 post-stimulus time windows: short latency (12.7 msec) middle latency (63 msec) and long latency (500 msec) using 3 different filter bandwidth.

The short latency VsEPs in humans is composed of several waves during the first 10 msec. The acceleration impulses in the plane of the horizontal SCCs activate one lateral SEE whereas the contralateral canal is inhibited. In the vertical plane the acceleration impulses excite both posterior SCCs whereas the anterior SCCs are partially inhibited. The first 2 waves (P1 & P2) of the short latency VsEPs are the most consistent and are probably originated in the vestibular nerve and nuclei, respectively.

The short latency VsEPs were missing in patients with bilateral peripheral vestibular loss and were abnormal in unilateral vestibular hypofunction. The middle latency VsEPs is dominated by a forehead positive peak at about 15 msec and a negative peak at about 20 msec, with peak to peak amplitude of about 30μv. This wave was shown to represent the "presaccadic spike" which proceeds the fast component of nystagmus and voluntary saccadic eye movements. It probably represents vestibular-initiated electrical activity in motor units of extraocular muscles, which produce compensatory or anitcompensatory saccades.

The vestibular activation by the acceleration impulses is not explained by the torsion pendulum model and is related presumably to direct excitation of the hair cells, which cause synchronized activity of irregular primary vestibular fibers.

**B17.3**
**The Horizontal VOR With Active and Passive Head Impulses After Unilateral Vestibular Deafferentation**
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We studied the horizontal VOR in response to active and passive yaw head impulses in human subjects after they had compensated for unilateral vestibular deafferentation. Passive head impulses are delivered by an experimenter; active head impulses are carried out by the subject. With visual feedback and practice subjects learn to make active head impulses that match the head velocity profile of passive head impulses. Head impulses are low amplitude (15-20 deg) medium velocity (150-350 deg/sec) high acceleration (4000-6000 deg/sec) head rotations. We found differences between the VOR with active as compared to the VOR with passive head impulses from the start of the response.

VOR gain measured at 75 msec from its onset was significantly higher in each direction during active than during passive impulses. Ipsilesional: ~0. 40 (active) vs ~0. 15 (passive); contralesional: ~0. 80 (active) vs ~0. 60 (passive). VOR latency was about 9 msec during active impulses and about 12 msec during passive impulses in either direction. Rapid compensatory eye movements that returned the eyes to Listing's plane and had the main-sequence characteristics of saccades, corrected the gaze error produced by the defective VOR. These eye movements appeared earlier in response to active(~ 75msec) than in response to passive head impulses (>250 msec).

These results show that when the subject tries to fix rather than re-fix gaze, the VOR is not turned off during active head rotations but is in fact enhanced.

**B17.4**
**Parametric analysis of high frequency active head rotation testing of the vestibulo-ocular reflex**
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We first described a method of active-head rotational testing of the vestibulo-ocular reflex (VOR) at the Barany Society meeting in Bologna in 1987. The protocol developed was for patients to perform 18 seconds of swept frequency active head movements while fixating on a wall-mounted target in the light, and wearing a head strap equipped with head and eye movement sensors. Horizontal and vertical head movements were performed in separate tests. Head and eye movement data were recorded and sent to a desktop PC. VOR gains and phases from 2-6 Hz were computed by spectral analysis for both horizontal and vertical VORs. We developed a commercial system based on this protocol called the Vestibular Autorotation Test (VAT122, Western Systems Research, Pasadena, CA). Our purpose is to describe updated software and hardware methods used presently with the VAT, and to summarize clinical interpretations useful for diagnostic screening of patients with balance disorders.

Physiological correction factors necessary for accurate results include 1) vergence-dependent gains for near-field targets, and 2) slippage of the headband during rapid movements. This requires correcting raw data points for accurate results. Broadband Fourier analysis techniques are used to account for mixed-frequency harmonics. Methods based on 01Cfitting01D single sinusoids to data segments, as used in rotational chair testing, produce inaccurate results, and are not used due to the harmonic complexity inherent in active head and eye movements.

Microchip and sensor advances during the past decade resulted in significant hardware and software upgrading. Data acquisition, filtering and transmission is performed with 14-bit microcontrollers programmed in C/C++. Head movements are monitored with MEMS-based micro sensors. Low-mass electrode clips and head-mounted instrumentation amplifiers are used to minimize artifacts during electro-oculographic recording. Data are transmitted to Windows-based notebook PCs using serial or USB ports for added portability.

Parametric modeling is used effectively to describe VOR system characteristics. These modern methods provide certain advantages over older, nonparametric methods. These include 1) reduction of spurious Fourier components at higher frequencies, 2) better overall test-retest reproducibility, and 3) model parameters that can be used for accurate comparisons and predictions.

Signature pattern combinations of VAT horizontal and vertical VOR gains and phases have been described for certain vestibular disorders such as systemic gentamicin ototoxicity, head trauma, BPPV and Meniere's disease. These will be summarized, and their use illustrated for monitoring patients undergoing vestibular rehabilitation.

**B17.5**

**High Frequency VOR in Healthy and Labyrinth Defective Subjects**

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The vestibulo-ocular reflex (VOR) generates eye rotations that compensate for head movements, thereby the VOR allows us to walk around and see at the same time. During locomotion the frequencies of head rotations are in the range of 0. 5 to 5. 0 Hz. To be able to generate eye movements that compensate for these high frequency head rotations, the brain has developed an effective system in which short latency pathways and highly sensitive sensors are key elements. However, despite the normal operating range of the VOR in the high frequency domain, sofar routine clinical testing of the VOR is done at low frequencies. This testing appears to be inadequate since the performance of the vestibular system is far from optimal in this frequency range. In addition, at low frequencies, also the visual system plays an important role in generating compensatory eye movements, confounding the role of the VOR. Because the visual tracking system has low-pass characteristics, its influence is negligible in the high frequency domain and thus we can test the VOR in isolation at high frequencies.

We tested high frequency VOR about the vertical axis in healthy subjects and patient groups with clinically bilateral strong vestibular hyporeflexia, with total or partial vestibular loss and transient clinical phenomena. We used a special torque helmet, which generates sinusoidal stimulation up to 20 Hz, or alternatively produces step-displacements. Eye movements were recorded with the scleral search coil technique. Two parameters, delay and gain were calculated from the slope and offset of the linear relation between eye and head velocities during the first 90 ms of the stimulation.

Normal subjects had a VOR gain of 0. 9 and a delay of 5 msec. Gain was lowered in one or both directions after unilateral or bilateral vestibular lesions. In addition, delay was prolonged in all subjects with vestibular pathology. We will discuss the significance of these results for clinical vestibular testing and future expansions of this technique to whole body oscillations and to off-vertical axis testing.

**B17.6**

**High acceleration testing of human semicircular canal function**

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Although each semicircular canal (SCC) functions in an asymmetrical fashion the vestibulo-ocular reflex normally functions in a symmetrical way. This is because any head rotation will change the activity from at least two SCCs, so that the brainstem signal which eventually drives the vestibulo-ocular reflex (VOR) is produced by direct excitation from one SCC and indirect disfacilitation from the other.

Direct excitation and indirect disinhibition are inherently asymmetrical. Although the discharge rate of a primary vestibular neuron can increase linearly without obvious saturation in response to a rapid yaw head rotation in the excitatory direction, it can decrease only to zero in response to a rotation in the disfacilitatory direction. Since most secondary SCC neurons have a lower resting rate and a higher sensitivity to angular accelerations than primary SCC neurons, they are even more easily silenced by rapid accelerations than primary neurons so that this inherent response asymmetry is even more marked at the level of secondary vestibular neurons.

Head impulses are rapid, passive, low-amplitude (10–20 deg), intermediate-velocity (120–180 deg/sec), high-acceleration (3000–4000 deg/sec$^2$), unpredictable rotations of the head with respect to the trunk. They are delivered by an examiner who rapidly rotates the subject's head in the yaw plane either to the left or to the right, or in the RALP or LARP plane, either forward or backward The subject fixates a target at 1 metre. To minimise any contribution from the cervico-ocular reflex, the visual pursuit reflex or the saccadic system, only those compensatory eye movement responses which occur in the first 150 msec after the onset of head acceleration are analysed.

In normal subjects, the horizontal VOR in response to yaw plane head impulses has a velocity gain of 0.94±0.08 (SD) at an arbitrary 122 deg /sec head velocity. In contrast the vertical-torsional VOR in response to RALP and LARP plane head impulses has a gain of only 0.7 to 0.8 because the gain of the roll-torsional VOR is lower than the gain of the pitch-vertical VOR.

Following uVD, the VOR in response to ipsilesional yaw plane head impulses is severely deficient; velocity gain saturates at about 0.20. In contrast, the VOR in response to contralesional yaw plane head impulses is only mildly deficient, with a velocity gain of 0.92. A high acceleration rotation saturates the ipsilesional horizontal VOR in the human and in the guinea pig just as it saturates the off-direction discharge rate of primary lateral SCC neurons in cat, monkey, rat and guinea pig.

Silencing of primary lateral SCC neurons in the contralesional vestibular nerve, leading to maximal disinhibition of type I secondary lateral SCC neurons in the ipsilesional vestibular nucleus is the main reason why a symmetrical head rotation stimulus produces an asymmetrical eye rotation response in a subject with only one functioning SCC and is also the reason why the magnitude of the response asymmetry is a function of the magnitude of the stimulus. Furthermore in response to high acceleration stimulation, excitation of a single lateral SCC can by itself produce a near-normal horizontal VOR. This suggests that in man as well as in the monkey, disinhibition of ipsilateral type I neurons from the contralateral lateral SCC makes only a small contribution to the horizontal VOR.

Following uVD the vertical-torsional VOR in response to RALP and LARP plane head impulses behaves similarly to the horizontal VOR. In response to head impulses toward the lesioned anterior or posterior SCC the VOR is severely deficient. This finding is confirmed after selective inactivation of one posterior SCC - in such patients the VOR is defective only in response to head impulses toward the occluded posterior SCC and is normal in response to head impulses toward any the other 5 SCCs.

**B18.1**

**Long-term plasticity in hippocampal NMDA receptor subunits following unilateral vestibular damage in the rat**

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Increasing evidence suggests that damage to the vestibular system causes abnormalities in hippocampal electrophysiology and neurochemistry. In this study we investigated the effects of unilateral vestibular deafferentation (UVD) on the expression of glutamate receptor subunits in subregions of the hippocampus, using western blotting.

Twenty eight rats, anesthetised with i. m. 300 µg/kg fentanyl citrate and 300 µg/kg medetomidine, were divided into UVD (n = 5), sham surgery (n = 5) and anesthetic control (n = 4) groups at 10 hs or 2 weeks post-op.

We found a significant decrease in NR1 expression in the ipsilateral CA2/3 region at 2 weeks post-op. compared to both the sham ($p < 0.02$) and anesthetic ($p < 0.05$) control groups. NR2A expression was significantly increased in the ipsilateral CA1 region at 10 hs post-op. , compared to both the sham ($p < 0.05$) and anesthetic controls ($p < 0.01$). At 2 weeks post-op. , NR2A expression was reduced in the ipsilateral CA2/3 region compared to both sham ($p < 0.05$) and anesthetic controls ($p < 0.05$). A similar decrease was found in the contralateral CA2/3 at 2 weeks post-op compared to the sham controls ($p < 0.05$). No significant differences were found in GluR2 expression in any area of the hippocampus at either time post-op.

These results suggest that UVD results in modifications of NMDA receptors in various subregions of the hippocampus, which could affect the ability of this region to support adaptive plasticity such as long-term potentiation.

**B18.2**

**Galvanic vestibular stimulation: fMRI and eye movement analyses**

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The effects of galvanic vestibular stimulation (GVS) were studied on (a) the cortical activation and deactivation patterns and (b) tonic and phasic torsional eye movements.

In a first experiment fMRI was used to measure multisensory cortical signal increases and decreases during GVS at the mastoid level in 13 healthy volunteers. Signal increases and decreases were compared during galvanic stimulation at different frequencies of sinusoidal stimulation (0.1 Hz, 0.3 Hz, 0.8 Hz, 1.0 Hz, 2.0 Hz, 5.0 Hz) in order to differentiate otolith-induced and semicircular-canal induced vestibular functions from ocular motor functions. Activations were found in anterior parts of the insula, the posterior insula, the parietal lobule, the precentral gyrus (frontal eye field), the middle frontal gyrus (prefrontal cortex), the middle temporal gyrus, the superior temporal gyrus, the anterior cingulated gyrus, and both cerebellar hemispheres. With higher stimulation frequencies the activated areas showed larger clusters. Activation sites and patterns were similar, the difference between low and high frequencies was not significant.

In a second experiment eye movements induced by GVS were analyzed by 3D-video-oculography (VOG). GVS is reported to induce interindividually variable tonic ocular torsion (OT) and superimposed torsional nystagmus. It has been proposed that the tonic component results from

the activation of otolith afferents, while the phasic component results from activation of the semicircular canals. We tested our hypothesis that both the tonic and phasic OT are mainly due to semicircular canal stimulation by determining whether the OT patterns elicited by GVS can be reproduced by pure SCC stimulations of a rotating chair. Therefore, the OT of six healthy volunteers was measured by VOG during application of two different stimuli (duration 20 s): 1) transmastoidal GVS steps of 2 mA with the head in a pitched, nose-down position and 2) angular head rotations around a combined roll-yaw axis parallel to the gravity vector with the head in the same position. Analysis of torsional eye movements under both conditions revealed no significant differences.

We conclude that both the tonic and the phasic OT responses during GVS are mainly related to the SCC afferents, since the responses are similar to those during natural rotational stimulations at small amplitudes. This explains why the activation pattern in fMRI does not change significantly during different stimulation frequencies.

**B18.3**

**Idiosyncrasy of the subjective visual horizontal after unilateral vestibular deafferentation**

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In peripheral vestibular lesions, the deviation of the subjective visual vertical (SVV) and subjective visual horizontal (SVH) is due to a tonic offset of torsional eye position and as such an indirect measurement of utricular function. We measured the SVV and the SVH in 65 consecutive patients before and 6 months after translabyrinthine surgery for vestibular schwannoma.

Method. Tumor size was measured with MRI and electronystagmography was performed including bithermal caloric tests, spontaneous and headshake nystagmus. The subjective visual horizontal and subjective visual vertical (SVH-V) was measured 4 times each and the mean was calculated. The patients were examined approximately 3 months before and 6 months after surgery.

Results. The mean SVH-V was 1.6 degrees before surgery and increased to 5.0 degrees after surgery ($p<0.001$) toward the ipsilesional side. The individual variation was great and SVH-V ranged from -3.8 to 13.4 before surgery and -2. 9 to 16.4 degrees postoperatively. Patient age, tumor size, the degree of pre-operative canal paresis or the presence of spontaneous or head-shaking nystagmus could not explain this variance. With linear regression analysis only 20. 3% of the SVH-V increase after surgery was explained by the SVH-V before surgery. 12.5% of the variance of the SVH-V before surgery was explained by the age of the patient. This might suggest an age-dependent delayed central compensation or perceptive changes or simply that the older patients had a difficult time understanding the instructions for the SVH-V test.

Conclusion. We propose that there is an idiosyncrasy of the SVH-V compensation after unilateral vestibular deafferentation and that it is not related to the general course of adaptation. This might be of importance for the chronic balance disturbances that some of these patients experience.

**B18.4**

**Perceptual stability during head movement**

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The perceptual world remains stable during voluntary rotational and translational head movements. How do the vestibular and visual sensory systems contribute to this sensation of stability? Translation and rotation components of self motion are detected by different patterns of optic flow and by different divisions of the vestibular system. A given movement can also involve different sensors depending on the orientation of the movement with respect to gravity. For example yaw rotation while sitting upright does not involve a change in orientation relative to gravity but does when supine. Similarly translation along the dorsal-lateral axis of the head add and subtract from gravity when standing up but not when supine. To measure the overall response to movement we exploited the fact that during a voluntary head movement the perceptual world normally remains stable. To achieve this requires knowing about the movement, especially about the movement of the eyes in space; predicting the expected visual movement of the world and comparing the actual and expected movements. We measured how much the visual world could be moved during head rotations and translations around various axes and still be perceived as visually stable. We looked for differences in performance that might correspond to the different sensors involved in a given movement.

Our subjects' task was to distinguish self produced visual motion from external visual motion during rotation around the yaw, pitch and roll axes and during translation in the naso-occipital, inter-aural and dorsal-ventral directions. The axis or direction of motion was arranged to be parallel or orthogonal to the direction of gravity. Subjects wore a head-mounted display (HMD). The HMD was updated in response to head movement which was monitored by a mechanical tracker. The ratio between head and image motion was varied. Subjects indicated whether the display appeared earth-stationary (perceptually stable) or appeared to move relative to the ground.

For both rotation and translation there was a large range of ratios of visual motion to head motion that was tolerated as perceptually stable. The ratio most likely to be accepted as stable corresponded to visual motion faster than head motion. For rotation there were no consistent differences between yaw, pitch or roll axes and the orientation of the axis relative to gravity also had no effect. For translation, motion in the naso-occipital direction was on average matched with less visual motion than inter-aural or dorsal-ventral motion.

There were no differences in judgments of perceptual stability performance that depended on whether the head motion was accompanied by changes of the head's orientation with respect to gravity. This implies a relatively small role of gravity in the perceptual response to head movement.

**B18.5**

**Vibration-induced shifts in the subjective visual horizontal -a sign of unilateral vestibular loss**

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Asking a subject in darkness to adjust a dimly lit bar to what he perceives as horizontal, the subjective visual horizontal test (SVH), is a simple and useful test for acute unilateral vestibular (possibly utricular) loss. It is less sensitive to chronic lesions. Vibrations to the head or neck excite both vestibular and neck muscle spindle afferents. Can such vibrations improve the sensitivity of the SVH test to chronic unilateral vestibular deficits?

Method. We studied 13 healthy subjects (mean age 32 years) and 23 patients (mean age 53 years) with chronic unilateral vestibular deficits after vestibular neurectomy or neuro-labyrinthitis. Head impulse test showed unilateral loss of all 3 semicircular canals in 14 patients and loss of only the anterior and lateral canals in 9 patients. SVH testing was performed without and during unilateral vibration (handheld vibrator, 92 Hz, 0. 6 mm amplitude) to the sternomastoid muscle or the mastoid bone.

Results. Without vibration all healthy subjects and 13/23 patients had SVH < 3 degrees (sensitivity 43%, specificity 100%). During vibration to the ipsilesional sternomastoid muscle SVH increased to > 3 degrees in 21/23 patients but only in 1/13 normal subjects (sensitivity 91%, specificity 92%). The patient group had significantly larger SVH shifts than healthy subjects in response to both sternomastoid muscle and mastoid bone vibration on either side. The vibration-induced SVH shift was significantly larger in patients with loss of 3 semicircular canals, than in those with loss of only 2.

Conclusion. The sensitivity of the SVH test to a chronic unilateral vestibular deficit can be improved by simply applying vibration to the sternomastoid muscle. The magnitude of vibratory SVH shift is related to the extent of unilateral deficit of the otolithic organs or the vertical canals or both, but not of the lateral canals.

**B18.6**

**Contribution of head and eye position to movement perception**

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It is well known that dynamic vestibular and proprioceptive inputs combine to internally reconstruct head and body position. Recently, we found that static proprioceptive information may also affect the beating field of optokinetic responses and body rotation perception. Therefore, we investigated the influence of cervical tonic deviation and eye position on space perception. We studied the rotation perception and the vestibulo-ocular reflex (VOR) in 10 subjects at different head-body angles and eccentric eye positions (± 22. 5° and ± 45). The subjects were seated on a Barany chair in darkness. Each trial began with the appearance of a spot, either straight ahead or in a 22°-45° eccentric position (right or left). The subjects were simply instructed to fixate the spot, that was switched off at the beginning of the chair oscillation. The oscillations were asymmetrical, the result of the combination of sinusoidal half cycles of the same amplitude but different frequencies (± 30° amplitude, 30% asymmetry and 0. 15 Hz frequency). The subjects were asked to remember spot position and to track it with their eyes as an imaginary target (imaginary pursuit) during chair swings. Their eye position was recorded by EOG throughout the stimulation period. In addition, VOR was also examined by rotating the subjects while they were trying to solve mathematical calculation.

It resulted that the imaginary pursuit was affected by both the head and eye tonic deviations. Four cycles of asymmetric oscillations caused a progressive shifting of the eye position towards the opposite side relative to the faster stimulation direction. The cumulative shift reached 20° at the end of the stimulation cycles in the straight head position. It increased to about 75° ± 24 when the head was 45° tonically deviated toward higher velocity stimulus, while it decreased (5° ± 30°) in the opposite head position. Conversely, when the subjects were tracking a target in the eccentric position with their head and trunk aligned, the final displacement of the eye was also affected, but oppositely. In fact, the eye shift was almost null with the eyes tonically deviated toward the high velocity stimulation side, while it was greater than 50° with opposite eye position. The VOR was also tested at different head and eye positions. The VOR gain was increased by about 0. 1- 0. 2 when the head was deviated towards the faster stimulation side, while decreased when the eye was deviated to this side.

We concluded that tonic head rotation enhances the perception of body rotation in the direction of the head position, while eye deviation enhances it in the opposite direction, and we suggest that changes in rotation perception may depend on the influence of eye and neck proprioception on the central process of vestibular input taking place at the level of the vestibular nuclei.

**B18.7**

**A Mismatch Between Visual and Vestibular Derived Displacement Alters Perception of Motion Duration**

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We hypothesised that since displacement may be derived by the time integral of the vestibular signal, then an observed visual displacement different from that expected on the basis of internal estimates of duration and velocity of motion, could affect the perception of these estimates.

Methods. 18 Subjects sat on a motorised rotating chair in which vision of the surrounding drum was allowed only at the beginning and end of motion. The drum was decorated with images separated by 22. 5deg. Unknown to the subjects, during some chair rotations the curtain was rotated. After each rotation, and prior to vision of the drum being allowed, subjects indicated their perceived position with an analogue indicator. Following a pair of rotations, subjects indicated if the first movement was longer or shorter in duration than the second. A pair of movements (raised cosine velocities of peak 20-90deg/s, duration 2-7s, and displacement 30-180deg) could either be of equal duration or differ by +/-1, 2, 3 or 4 seconds presented in balanced unpredictable sequences. There were 10 baseline trial pairs where the drum was stationary. In 20 subsequent trial pairs, the drum rotated during one of the subject movements per trial pair by amplitudes up to 100% of those of the chair. Thus, e. g. a drum rotation in the same

direction as the subject was intended to make the rotation seem shorter in duration since when the light came on the subject would see that he had apparently made a smaller angular displacement.

Findings. The probability of subjects making a correct comparison of duration of baseline rotations was 0. 9. With drum rotations, the probability of making correct comparisons of rotation durations were 0. 1 for 1s ($p < 0.0001$) and 0. 82 for 3s ($p=0.014$); i. e. shorter durations were made to appear longer by false feedback of displacement and vice versa for time differences up to 3s (but not for 4s which was not different from control). Subjects developed no suspicions that the drum rotated and made the required comparisons with ease.

We performed a similar experiment except that we gave movements of differing peak velocity and asked subjects to say which rotation was faster. When analysed for peak velocity, perturbed visual-derived displacement had no influence on subjects' responses compared to control. When analysed for acceleration we found a similar (and significant) effect as we did for duration of motion.

Comment. That static visual information can recalibrate the internal perception of time, vestibularly-derived displacement and peak acceleration, has not been previously shown in humans (static visual cues recalibrate rat head direction cells). The perception of small differences between movement durations may be influenced by visual recalibration of the already integrated vestibular signal. This influence may compete probabilistically with other systems that generate an internal estimate of time. Our data also suggests that perception of velocity is veridical whilst that of displacement and acceleration is not. These latter percepts may be derived by cortical processing of the ascending brainstem velocity signal.

**B18.8**

**Anxiety and vertigo : A Pharmacological approach**

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In 01CICD-10, Classification of Mental and Behavioural Disorders, the complaints of vertigo and dizziness are noted in the neurotic stress-related and somatoform disorders and in depression. It has been suspected that the abnormal re-absorption of the serotonin in the hippocampus induces anxiety and/or depression.

The purpose of this clinical study is to clarify why patients with anxiety disorders complain of vertigo. In this study, we took those patients who complained of vertigo but who had neither anxiety disorders with no history of the vestibular disease nor had abnormalities detected by the otoneurological examinations. Those who already had taken the drugs, which affect the central nervous system, were excluded. Total number of the patients was 45 (39 female 6 male). Mean age was 54. 1 raged 31 to 69. These patients were given Fluboxiame tablet 25mg (i. e. the selective serotonin re-absorption inhibiter) two times per day.

The patients were asked about the existence of vertigo 2 and 4 weeks after. The vertigo disappeared in 67% of the patients after 2 weeks, in 97% after 4 weeks. In a recent study using rats, Winner et. al. reported that serotonin is the neuron transmitter related directional cells in the hippocampus. Regarding this finding and our results, the abnormal re-absorption in the hippocampus provokes not only anxiety but also the feeling of the vertigo.

**B18.9**

**Clinical and neuro-otologic findings in acute migrainous vertigo**

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Migrainous vertigo (MV) is an increasingly recognised cause of episodic vertigo. The pathophysiology of MV is still a matter of speculation and it is not known whether the dysfunction is located in the central or peripheral vestibular system. In this prospective study we systematically examined patients with MV during acute episodes. Specifically, we wanted to know which structures of the vestibular system are involved in MV.

Patients diagnosed for MV according to strict criteria (Neuhauser et al. 2001) were examined during an acute episode and the asymptomatic interval. Testing included a neurologic and neuro-otologic examination, recordings of spontaneous and positional nystagmus with 3D-video-oculography and audiometry.

15 patients (10 female, 5 male, age 18 to 70 years) were included in the study. All patients, except for one, had migrainous symptoms during the documented episode, most often photophobia (n=12) and headache (n=9). Vestibular symptoms were positional vertigo (n=6), permanent vertigo (n=5) or head motion intolerance (n=4). Pathologic nystagmus was observed in 80% of patients during acute MV. 5 patients had spontaneous horizontal nystagmus with a slow phase velocity (SPV) ranging between 3. 6 and 42°/s: 3 patients showed a contralateral deficit of the horizontal vestibulo-ocular reflex during rapid head rotations, indicating peripheral vestibular dysfunction. Spontaneous upbeat nystagmus (SPV 6. 2°/s) was observed in 1 patient and torsional nystagmus (SPV 13. 5°/s) in another. In 4 patients persistent positional nystagmus beating in the vertical, horizontal or torsional plane could be observed. Finally, torsional nystagmus was evoked in 1 patient by horizontal head shaking. Saccades were normal in all patients and 2 patients showed saccadic pursuit. Imbalance was noted in all patients except one. Audiometry identified mild-moderate bilateral hearing loss in 2 patients both during the attack and the interval.

Findings during acute MV pointed to a central-vestibular dysfunction in 8 patients (53%) and to a peripheral vestibular dysfunction in 3 patients (20%); in 4 patients the site of the involved structures could not be determined with certainty.

MV should be considered in the differential diagnosis of vertigo with spontaneous and positional nystagmus and can present both as a central and a peripheral vestibular disorder. Consequently, it is likely that various pathomechanisms can be involved in MV.

**B19.1**

**Effects Of Unilateral Vestibular Deafferentation On The Linear VOR Evoked By Eccentric Roll Rotation**

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The vestibulo-ocular reflex (VOR) generates compensatory eye rotations that stabilize vision during head movements. To study the effects of unilateral vestibular deafferentation (UVD) on the linear VOR, we measured the three-dimensional eye movement responses of UVD subjects evoked by impulsive eccentric roll rotation and compared their responses to normal subjects. The stimulus, a whole body roll rotation with the eye positioned 815 mm eccentric to the rotation axis produced a peak inter-aural linear head acceleration of ~0. 55 g and roll peak angular head acceleration of ~360º/s2. At peak linear head acceleration, the head had only rotated in roll by ~0. 5º. During the stimulus, the subjects fixated on a target positioned at either 200, 300 or 600 mm. The response to this stimulus comprises horizontal eye rotations generated by the linear VOR and torsional eye rotations generated by the angular VOR.

Linear VOR acceleration gain, defined as the slope of actual horizontal eye velocity divided by the slope of ideal horizontal eye velocity during a 30 ms period starting 70 ms from stimulus onset, was bilaterally and symmetrically reduced in UVD subjects to about half normal value. In the first 100 ms of this response, linear VOR enhancement by near viewing was still present in UVD subjects. Linear VOR latency for 200, 300 and 600 mm viewing distances was ~38 ms in UVD subjects and ~33 ms in normal subjects. There was no significant difference between the latency in UVD subjects to that in normal subjects for each viewing distance.

These results show that the linear VOR produced by a single functioning labyrinth after UVD is bilaterally and symmetrically reduced to about half normal, but the response characteristics such as latency and modulation by viewing distance remain unaltered. After UVD, whereas the angular VOR is highly asymmetrical with a much larger ipsilesional than contralesional deficit in response to an impulsive head rotation, the linear VOR is symmetrical with similar response deficits to both the ipsilesional and contralesional sides. This difference between angular and linear VOR could reflect the difference in hair cell polarizations between the semicircular canals and otoliths.

**B19.2**
**Human Surge Linear Vestibulo-Ocular Reflex (LVOR) with Vertically Eccentric Targets**
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Visual fixation during anteroposterior translation (surge) requires an LVOR dependent both on target direction and target distance. We subjected normal and unilaterally vestibularly deafferented (UVD) humans to transient surge with targets above and below the motion direction to evoke a vertical LVOR.

Transients of 0. 5 G peak whole body surge acceleration were delivered by a pneumatic servo on which were seated 9 normal adults (mean ± SE age 28±2 yrs) and 7 subjects (age 60±4 yrs) with chronic UVD by labyrinthectomy or neurectomy. Eye rotation was sampled at 1,200 Hz using a dual winding search coil on one eye, and a single winding coil on the other. Head acceleration was measured by a bite bar accelerometer. Immediately before surge onset in darkness, subjects viewed a luminous target 25 or 50 cm from the interocular midpoint, and either centered, or displaced 10 degrees upward or downward. The target was extinguished 30 to 60 ms before randomly varied onset of 10 surges for each condition. Surge direction was randomized for the 50 cm target, but was always aft for 25 cm to avoid collision. LVOR velocity gain was determined 100 to 200 ms following surge onset as percentage of geometric ideal. In all subjects, there was a relatively low gain horizontal LVOR for all target positions, while with vertically eccentric targets there was also a higher gain vertical LVOR. Forward surge evoked convergence, and aft surge evoked divergence, with absolute magnitude greater, but gain less, for the 25 than 50 cm target. Target distance had less effect on the vertical LVOR gain component. For the upper target, forward surge evoked a slow phase upward LVOR, while aft surge evoked a downward LVOR. For the lower target, forward surge evoked a downward LVOR, while aft surge evoked an upward LVOR. Although absolute response magnitude was greater for the 25 than 50 cm target, vertical gain remained similar.

For the 50 cm distance and aft motion, upward target slow phase gain in normal subjects was 0. 78±0. 15, while downward target gain was 0. 76±0. 10; in UVD subjects, upward target gain was 0. 25±0. 04 while downward target gain was 0. 61±0. 08. At 25 cm, upward target slow phase gain in normal subjects was 0. 87±0. 12, while downward target gain was 0. 59±0. 09; in UVD, upward target gain was 0. 52±0. 01 while downward target gain was 0. 51±0. 05. Latency of this vertical LVOR was 47±4 ms in normal subjects, but significantly prolonged to 82±8 ms in UVD ($P<0.001$). In addition to the slow phase LVOR, subjects often made compensatory saccades with latencies as short as 50 ms. In both subject groups, gain was higher under comparable conditions when the target remained visible.

Normal and UVD subjects exhibit a slow phase vertical surge LVOR that depends on vertical target location, often augmented by saccades. Gain was similar but latency almost doubled in the UVD group, whose greater age might have contributed to the prolongation.

**B19.3**
**A Comparison of Ocular Counterrolling in Naso-Occipital and Barbecue Rotations**
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When a person is lying in bed on the right side, for example, theoretically it should make no difference in eye torsion if this position was achieved by rolling over from a supine position or by tilting sideways from a seated position. In other words, is ocular counterrolling (OCR) the same if rotation to 90 degrees occurs in the naso-occipital (N-O) axis as in the Earth-horizontal (BBQ) long axis?

A number of years ago, we looked at this question and found no significant differences in OCR either in the process of rotation to 90 degrees or in the terminal position. Since that time, technology has enabled a much more precise examination of OCR; hence, we repeated the study

using SensoMotoric Instruments' VOG apparatus, which has the capability of video recording 25 images/sec binocularly and analyzing them with an accuracy of 0. 1degrees.

Subjects were strapped into a motorized chair, heads immobilized with a bite bar, mask containing two video cameras attached, and rotated twice about their naso-occipital axis to 90 degrees right and left. The chair was then repositioned with subjects face-up and then rotated twice about their now Earth-horizontal long axis to 90 degrees right and left. Two minutes of baseline recording was performed before the beginning and at the end of each mode of rotation. Subjects remained strapped in position during changes of chair orientation. Chair velocity was 3 degrees/sec, with accelerations and decelerations of 0. 2 degrees/sec, below the threshold of the semicircular canals.

Results in 9 subjects showed greater mean OCR amplitude in N-O, 4. 27degrees, (1. 39 degrees SD) than in BBQ, 3. 52 degrees (1. 43 SD). Disconjugacy, the torsional difference in the two eyes at each observation, was also measured. Mean disconjugacy was greater in BBQ, 1. 43 degrees (0. 77 SD) than in N-O, 67 degrees (. 30 SD). In sum, there was less amplitude and more disconjugacy in BBQ than in N-O rotation.

To rule out that these results were the effect of order of presentation, four subjects were retested in the reverse order of rotation, BBQ first followed by N-O. In this limited sample, amplitude and disconjugacy were virtually the same in both modes of stimulation. Further studies are underway to clarify this apparent contradiction. Fatigue seems not to be a factor; earlier studies showed no diminution of response after four trials of N-O rotation. Pitch has long been known to stimulate otolith units but is not considered to be an effective stimulus to OCR. The procedure to achieve BBQ position was not a pitch maneuver per se, but the nose-up position is in fact the head orientation of a pitch position.

**B19.4**

**Vestibular Evoked Myogenic Potentials in the neck extensor muscles of Rat**

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Vestibular evoked myogenic potentials (VEMPs) are regarded as a new useful clinical test of the vestibular function in human, but they have not been recorded from animals. The purpose of this experiment is to establish in stable recording of the VEMPs from experimental animals under both acute and chronic recording conditions, and to find out useful parameters for the vestibular abilities.

Methods. We recorded the VEMPs from neck extensor and flexor muscles of rats by a pair of hooked silver (Ag-AgCl) electrodes. We used eight rats in the chronic experiments. Under pentbarbital sodium anesthesia, we performed labyrintecromy on the right ear, planted recording electrodes for auditory brain stem responses (ABR) and VEMP, mounted connector for preamplifier on the head of animals by dental cement in advance for daily recordings. After the operation, we recorded ABR and VEMP once a day under free field condition in a sound proof room. Stimulation was applied by speaker located 40 cm above the animal. In another experimental condition, we used decerebrated 13 rats (130~240g) for acute experiment. In acute animals, sound stimulation (1000Hz tone burst) were applied to a test ear, while bound pass noise were applied to another ear by earphones through polyvinyl chloride tubes. The stimulation rate was 5 Hz (acute) and 2 Hz (chronic), and the analysis time 20 msec. The responses to 200 stimuli were averaged. ABR were recorded by needle electrodes, and was performed before VEMP record to determine on the auditory threshold.

Results. Double phase myogenic responses (negative and positive waves) were recorded from the neck extensor muscles, while were not recorded from the flexor muscles. The responses were dominant in ipsilateral muscles. Mean threshold of the responses revealed 86. 7 dB SPL, while that of ABR reveals 39. 0 dB SPl. The latencies raged 3. 4 - 4. 1 msec, which changed by strength of stimulus, and prolonged around the threshold. These myogenic potentials were similar to VEMP in human. First, threshold of the response was around 80 - 85 dB, which was higher than ABR threshold by 40 - 45 dB. Second, the response could be only recorded in very high spontaneous activity muscles. Third, the latency was shorter than the startle reflex, and adaptational phenomena were not observed.

These myogenic responses may useful for testing the vestibular function in animals. Latency of the response is good parameter for analyzing the vestibular functions.

**B19.5**

**Molecular changes in the rat peripheral and central vestibular systems following hypergravity**

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Recovery from balance disorders after space flight is supposed to reflect the process of readaptation to 1G environment from microgravity. Linear acceleration including gravity is sensed by otolithic pathways. Therefore, it could be assumed that possible plastic changes which have influences on the otolithic pathways from the level of the vestibular periphery to the level of neurotransmission in the central vestibular system might be responsible for the adaptation to altered gravity.

The aim of the present study is to clarify the mechanisms responsible for the adaptation to altered gravity by examining the molecular biological changes in the rat peripheral and central vestibular systems following hypergravity (2G). Hypergravitational environment was produced by a centrifuge device. For this purpose, we investigated the changes in morphology and synthesis of otoconia and mRNA expression of various glutamate receptor subunits/subtypes in the vestibular ganglion cells, vestibular nuclei and vestibulocerebellum following hypergravity using real-time quantitative PCR methods.

The results showed that neither morphology nor synthesis of otoconia was affected by hypergravity, suggesting that otoconia itself has only minor role in the adaptation to altered gravity. The mRNA expression of GluR2 and NR1 receptors in the uvula/nodulus increased in animals exposed to 2 hs-hypergravity, and it decreased gradually to the control level. The mRNA expression of GluR2 receptors in vestibular ganglion cells decreased in animals exposed to 1 week-hypergravity. It is suggested that the animals adapted to the hypergravity by enhancing

the cerebellar inhibition of the vestibular nucleus neurons through activation of the NR1 and GluR2 receptors on the Purkinje cells in uvula/nodulus especially at the early phase following hypergravity. In the later phase following hypergravity, the animals adapted to the hypergravity by reducing the neurotransmission between the vestibular hair cells and the primary vestibular neurons via down-regulation of the post-synaptic GluR2 receptors in the vestibular periphery. (supported by Japan Space Forum and the National Space Development Agency of Japan)

**B19.6**

**Otolith Neurons Distinguish Between Translations and Tilts**

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We studied responses of 31 neurons in a squirrel monkey's vestibular nuclei to sinusoidal 3-dimensional rotations (yaw, pitch, roll) and translations (Inter-Aural, IA; Naso-Occipital, NO; Dorso-Ventral, DV). At 1. 2 Hz two neurons responded primarily to rotations, 13 primarily to translations while 16 responded to both. Six of the latter were eye movement-related neurons whose responses during the linear vestibuloocular reflex (LVOR) and smooth pursuit were closely related to the eye velocity produced.

This report focuses on the 13 neurons that responded only to translations at 1. 2 Hz. We classified these as otolith neurons. Two otolith neurons responded preferentially to NO motion, one to DV and 10 to IA. 5/13 exhibited acceleration responses, 3 velocity responses, 2 hybrid responses with sensitivities related to acceleration but velocity phases. Three exhibited spatio-temporal convergent responses.

Lack of a significant response to pitch and roll rotations at 1. 2 Hz could simply reflect the fact that these rotations had amplitudes too small to elicit a detectable response related to reorientation of the head with respect to gravity. We therefore compared responses to 0. 3 Hz translations and rotations with amplitudes that produced similar sinusoidal modulations of linear acceleration. The response to pitch tilt was compared with the response to NO translation in one NO preferring neuron. It was 1. 9 times as sensitive to NO as to pitch and its response to pitch was in the opposite direction to that predicted from its NO response. Responses to roll tilt and IA translation were compared in 8 neurons preferentially sensitive to IA motion. Six of these were 2 - 25 times as responsive to linear accelerations produced by translation as to accelerations related to changing head orientation with respect to gravity. The primary response of one neuron to 0. 3 Hz roll was an angular position-related response that appeared only at 0. 3 and 0. 6 Hz. This signal could be summed with the incoming otolith afferent signal in order to cancel the tilt-related portion of the otolith afferent response yielding a pure translation signal.

Thus our data provide clues about how the CNS is able to distinguish between translations and tilts.

**B19.7**

**Do Ribbon Synapse Size Differences in Macular Hair Cells Indicate Synaptic Efficacy**?

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In a significant finding, Magee and Cook (2000, Nat. Neurosci. 3:895903) observed that that synaptic strength is location dependent in pyramidal neurons (there is upscaling of synaptic conductance with distance). That is, synapses located more distally on a dendritic tree initiate local EPSPs of higher amplitude than do more proximally located synapses. Could this be related to the size of the synapse? It has been suggested that larger synapses are also more effective (FA Edwards, 2000, Physiol. Rev. 73: 759). In vestibular maculae of the rat, ribbon synapses in type II hair cells are larger as well as more numerous than those in type I cells. Type I hair cell ribbon synapses, typically found near or at the base of the hair cell, communicate with calyces. Type II hair cell ribbons typically synapse more distally, with branches of calyces, although some synapses are with the outer membrane of a calyx and a few ribbons communicate directly with primary afferents. Size differences in ribbon synapses of the two kinds of hair cells were determined from macular tissues used in prior space experiments (SL-1, SL-2 and Neurolab).

Because ancillary transmission electron microscope (TEM) software for measuring ribbon size in the TEM was not available during these prior studies, current measurements are based on transmission electron micrographs taken at 12,000X -20,000X magnification enlarged to ~30,000X to ~50,000X. Results indicate that synaptic rods in type II cells are ~33% longer and ~80% wider on average than those in type I hair cells. In the case of synaptic spheres, spherules in type II hair cells were ~53% larger in diameter. Size differences correlate with the number of vesicles available to the larger synaptic site. There are also numerical differences in ribbon synapses between the two maculae. In the Neurolab tissues, where a comparison can be made, the mean number of synapses in Basal utricular type I cells was 2. 034 and, in type II cells, 4. 744. In Basal type I saccular hair cells the mean was 4. 133 and, in type II cells, 7. 934. Statistical analyses are still to be completed.

The results indicate anatomical constraints in dynamic peripheral information processing that should be taken into account in functional interpretations. The size/numerical differences may serve to equalize synaptic efficacy within the network, or to provide a shunting mechanism that favors proximal (type I cell) synapse efficacy (M London and I Segev, 2001, Nat. Neurosci. 4:853). (This research was supported by a NASA and by Grant #47305 from the National Institute of Mental Health. )

**B19.8**

**Modulation of vestibular head-shaking nystagmus by gravity**

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Patients with acute unilateral peripheral vestibular deficit avoid lying on their affected ear, since, in this body position, symptoms become more severe and spontaneous nystagmus (SN) increases. It was hypothesized that this phenomenon is due to a reduced ipsilesional otolithic inhibition of asymmetric semicircular canal signals. Over time, adaptation normally reduces SN, but a residual

vestibular asymmetry can still be demonstrated by head shaking. We asked whether head-shaking nystagmus (HSN) in patients with chronic unilateral deficit due to vestibular neuritis is influenced by gravity in a similar way as SN in acute patients.

Using a three-dimensional (3D) motorized turntable, patients (N = 7) and healthy subjects (N = 12) were placed in different whole-body positions along the roll plane and oscillated about their head-fixed vertical axis (1 Hz, ± 10 &#186). Ocular drift was recorded with 3D magnetic search coils. In all patients, HSN was modulated by gravity: when lying on the affected ear, ocular drift was significantly increased by head shaking ($p < 0.01$), while this was not the case in the upright position and the healthy ear-down position ($p > 0.05$). In the affected ear-down position, the increase of slow-phase velocity by head shaking was restricted to the horizontal component and consisted of a drift towards the affected ear (average: 1. 2 &#186/s ± 0. 5 SD), which was added to gravity-independent and directionally nonspecific SN.

Conclusion. HSN in patients with chronic unilateral peripheral vestibular deficit is best elicited when they are lying on their affected ear. This suggests a gravity-dependent mechanism that is similar to the one found for SN in acute patients. The unmasking of asymmetric semicircular canal signals by head shaking is probably due to an asymmetric dumping mechanism of the horizontal vestibulo-ocular reflex via the cerebellum as a result of a one-sided reduction of otolith function. (Supported by Swiss National Science Foundation (32-51938. 97 / 31-63465. 00), and Koetser Foundation for Brain Research, Zurich, Switzerland).

**B19.9**

**Pharmaceutical countermeasures for space motion sickness and their effect on the otolith and canals**

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A mismatch between utricular and semi-circular canal output is believed to provoke space motion sickness. To assess the utricular and the horizontal canal functions, we apply the unilateral otolith test (UOT) (see abstract by Wuyts et al) and the standard electronystgmograpic (ENG) test battery. We use a modified paradigm of the unilateral otolith test during which the subject is rotated about an earth vertical axis at a velocity of 400 deg/s and 4 cm translated along an interaural axis to the right and to the left. When the axis of rotation is positioned through one utricular system, only the contralateral utricle is stimulated. Consequently, the centrifuged utricle 01Cfeels01D an outward pulling force equal to 0.4g, corresponding to a gravito-inertial acceleration (GIA) tilt of 21 degrees. This utricular stimulation induces an ocular counter rolling (OCR), that is measured on-line using validated three dimensional video-oculography.

For analysis of the experimental data, we use a theoretical model proposing a linear relationship between the OCR and the GIA tilt felt by a transducer placed at the centre of the head, behind the subject: (OCR = intercept + slope x GIA tilt). The function of each utricle is assumed to be additive. The slope of the linear regression is a measure of the responsiveness of both utricles whereas the intercept is a measure of lateralisation. These results are presented in the framework of a study 018Pharmacological countermeasures for space motion sickness (NSBRI / NASA grant: #NCC9-58019), the aim of which is to assess the effect of promethazine, scopolamine, lorazepam and meclozine in healthy subjects. We present here preliminary results of promethazine 25 mg and scopolamine 0. 4 mg.

Material and methods. Nine healthy volunteers (five female, four male) with an average age of 27. 1 year (21-47 years) were recruited. All subjects had three sessions: one control session (UOT and ENG) one week prior to the intake of the drug, one session with UOT and ENG at the maximum response of the drug and one control session with UOT one week later.

Results. Wilcoxon Matched pairs signed rank test indicates a significant decline in utricular responsiveness after intake of promethazine ($p = 0.044$) in reference to the control measurements. The effect on the horizontal canal responsiveness is even stronger ($p = 0.012$ for the caloric sum and $p=0.012$ for the gain on rotation). Scopolamine however, has no significant effect on the utricular responsiveness ($p = 0.16$). The effect on caloric sum and gain are however significant ($p=0.012$ each).

Conclusion. Our results indicate that intake of promethazine leads to a suppression of the utricular function, a declined responsiveness of the horizontal semicircular canals and also to central inhibition. On the other hand, scopolamine does not reduce the utricular sensitivity, although it induces central inhibition as well as a significant decline in horizontal semicircular canal function.

**B19.10**

**Adaptation of the Vestibulo-Ocular Reflex, Subjective Tilt, and Motion Sickness to Head Movements During Short-Radius Centrifugation**

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We report evidence of adaptation of the vestibulo-ocular reflex (VOR) for head movements made while rotating. Such adaptation is indispensable when an observer's sensory environment is systematically changed, such as in weightlessness. Head movements made in the unusual environment of a short-radius (2 m) rotator, with head near the center and feet at the rim, produce strong conflicts among vestibular, visual and proprioceptive information. These conflicts, in turn, result in inappropriate eye movements, sensory illusions, disorientation and oftentimes motion-sickness. We investigated the sensory adaptation of humans to this conflict by repeatedly exposing eight subjects to horizontal rotation at 23 rpm over an eight-day period. The dependent measures were inappropriate vertical VOR, subjective tilt, and motion-sickness in response to 90 degree yaw out-of-plane head movements. Motion-sickness was evaluated during and following exposure to rotation. Significant adaptation effects were found for the slow phase velocity of vertical nystagmus, the reported magnitude of the subjective tilt experienced during head turns, and motion-sickness scores. Retention of adaptation over a six-day rest period without rotation occurred, but was not complete for all measures.

Adaptation for VOR was completely maintained while subjective tilt was partially maintained and motion-sickness scores continued to decrease. Practical implications of these findings for artificial gravity will be discussed.

**BP1.1**

**The Interutriculary Distance Measured on MRI in 50 subjects**

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The knowledge of the distance between the utriculi plays an important role in the unilateral otolith testing (UOT). During this UOT subjects are rotated at high velocities (e. g. 400 deg/s) and then simultaneously displaced laterally along an interaural axis so that one utricle becomes aligned with the rotatory axis. When the axis of rotation crosses precisely through one utricle, only the other utricle will be stimulated, leading to an ocular counter rolling. Therefore, it is of importance to know the distance between both utricles.

The main purpose of this study is to measure this interutriculary distance (IUD) and to demonstrate the existence of a relationship between the IUD and external measures of head dimensions. With this information we can predict the IUD in individual subjects by measuring the appropriate outside parameters.

Material and methods. A group of 50 subjects (25 female, 25 male) was tested. In all subjects an MRI examination of the brain and skull base was performed (0,8 mm slice thickness). The following distances on the MRI images were measured: interpupillary distance, distance between the margo lateralis orbitae, the distance between the lateral margins of the vestibulum (posterior part) as a measure for the IUD, the total width of the head (measured between the tabulae externae at the level of the juncture of the auricle and the head) and the distance between the lateral semicircular canals and the ipsilateral tabula externa.

In all subjects, external parameters were measured using a caliper (measurement error 0. 35%): distance nasion-ilion, distance between the mastoids, distance between the temporomandibular joints, distance between the margo lateralis orbitae. We used a pupillar-distance-meter to measure the interpupillary distance. Length and weight of the subjects were also determined. Using multiple linear regression analysis (SPSS V10), we investigated which combination of the external measures could predict the IUD with appropriate accuracy.

Results. Since men and women have different head sizes, the analysis was performed for both sexes separately. The average IUD ± se on MRI yields IUDmen = 8. 05 ± 0. 06 cm (N=25) and IUDwomen= 7. 56 ± 0. 06 cm (N=25). This implies that the lateral displacement along the interaural axis, so that one labyrinth becomes aligned with the rotatory axis, should be 4. 02 cm for male subjects and 3. 78 cm for female subjects.

To personalize the distance in each individual subject, the following multiple linear regression equations were obtained: for male subjects: IUD = -1. 2 + 0. 53*(Distance between mastoids (10-2 m)) + 1. 06*(Length (m)) with an r2 = 0. 57 and for female subjects: IUD = -1. 1 + 0. 47*(Distance between mastoids (10-2 m)) + 0. 15*(Distance between the lateral margins of the orbitae (10-2 m)) with an r2 = 0. 67.

Additionally we investigate the position of the vestibular systems in the head with respect to the head center, so as to determine a measure of eccentricity. We observed that the asymmetry for both sexes appears to be within 4%.

**BP1.2**

**Regulation of endocytosis in the epithelial cells of the endolymphatic sac**

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Endocytosis is a highly dynamic process, which is regulated by various stimuli and signals, e.g. small GTP-binding proteins, coat proteins, dynamin. In the polarized epithelial cell, where the surface membrane is divided into two domains of distinct composition, continual endocytosis and recycling occur. In the renal collecting duct, endocytosis plays an important role in absorption of water. Also in the endolymphatic sac, endocytosis appears to regulate the activity of transport systems.

We investigated how endocytosis in the endolymphatic sac was regulated by alterations in extracellular circumstances using cultured rat endolymphatic sac epithelial cells. The effects of changes in time course, pH, osmotic pressure, temperature, potassium ion concentration, and administration of bafiromycin A1, and isoproterenol were investigated using FITC (fluorescein isothiocyanateas)-dextran as a probe for endosome function and localization. FITC-labeled vesicles were observed and quantitative analysis was done by fluorescence microscopy. FITC-dextran began to be internalized in endosomes after 3min and the internalization of FITC-dextran in endosomes leached maximum level after 15 min in basic culture medium.

Hypotonic solution, potassium ion depletion, and cholera toxin decreased endocytotic activity . Flow rate of endolymph toward the endolymphatic sac (longitudinal flow) is thought to be relatively slow. However, the epithelial cells of the endolymphatic sac showed very rapid endocytotic activity and response to various changes in extracellular circumstances. Our data suggest that the endolymphatic sac epithelial cells have potential which can transport membrane proteins, chemicals, cell debris and fluid more rapidly and locally in the endolymphatic sac than has been thought until now.

**BP1.3**

**The effect of age on type I and type II vestibular hair cell counts in the human crista ampullaris**

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Objective. To determine the effect of age on the total number of hair cells and supporting cells in the human peripheral vestibular sensory epithelia from subjects with

normal vestibular function.

Methods. Temporal bones were obtained post-mortem from normal patients (n=16) with well-documented clinical records (age range 26-98 years). The horizontal crista ampullaris was microdissected and embedded in plastic; 2-micron thick serial sections were made. Estimates of total hair cell counts were obtained using the unbiased stereology-physical fractionator technique (Fernandez et al. J Neurophysiol, 73,1253-1269, 1995; Lopez et al. Int J. Dev. Neurosci 15,447-461, 1997). To determine regional variations in the human crista the neuroepithelium was divided into peripheral, intermediate and central areas according to Fernandez et al. (1995).

Results. In the crista from younger subjects (26-57 years old), there was an average of 3583±158 type I hair cells, 3416±166 type II hair cells and 8358±302 supporting cells. There was a significant decline in hair cells counts in older individuals (90-98 years); there was an average of 2607±250 type I hair cells, 1628±124 type II hair cells and 8055±194 supporting cells. In the older individuals, there was a 20% loss of the total number of hair cells as compared with the younger individuals: a 27% loss of type I hair cells, and a 52% loss of type II hair cells. Supporting cells counts were unaffected by age. Hair cell distribution by zone: in the younger individuals type I hair cells were distributed as follow: 42% in the periphery, 30% in the intermediate and 28% in the central zone. Type II hair cell distribution was similar to type I hair cells, 42% in the peripheral, 31% in the intermediate and 27% in the central zone. In the older individuals hair cells distribution was similar to the younger individuals: 42% in the periphery, 30% in the intermediate zone and 28% in the central zone. Type II hair cells: 37% in the periphery, 34% in the intermediate and 29% in the central zone. These data suggest that hair cell loss with age occurs uniformly through the entire crista neuroepithelia.

Conclusions. The results demonstrated a steady decline in the vestibular hair cells, type II greater than type I, with increasing age. These results have important implications regarding the etiology of dysequilibrium of aging. (Grant Sponsor: National Institutes of Health grants DC 00140-02 and AG 09693. )

**BP1.4**

**Vestibular Morphology in the mutant Mix-mice**

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A new strain of mice with inner ear dysfunction, the so-called mix-mouse, has developed as the result of a spontaneous mutation. The mix-mouse, arising from a population of mice bred for their temperament and color, is born with typical signs of inner ear dysfunction, being deaf and showing a circling behavior and head-tossing movements. Morphological information about the vestibular part of the inner ear is missing. This is to our knowledge the first study to describe the pathological anatomy of the vestibular end organs.

Materials & Methods. A total of 7 mix-mice were morphologically analysed. The mice were checked clinically in their cages for circling behaviour and lack of reaction to sound using the Preyer reflex. Three non circling litter-mates and 4 normal CBA mice were used as controls. After sacrifice, the temporal bones were dissected and the cristae ampullares, macula utriculi and sacculi were removed. They were fixed with 3% glutaraldehyde in PBS. The specimens were then embedded in agar and further preparations for light microscopy (LM) and transmission electron microscopy (TEM) were performed according to standard methods.

Results. The normally behaving litter-mate, by LM, only showed minor degeneration of nerve chalices surrounding type I hair cells. By TEM, it was possible to detect that the hair cells in all sensory epithelia showed surface herniations and so-called “blebs” in the apical portion of the epithelium. It is evident that the sensory hairs demonstrated a disarrayed pattern. The microvilli on the supporting cells were characteristically present.

The mix-mice demonstrated more severe abnormalities. In the ampulla, collapse of the membranous cell layer constituting the ampullary roof was frequently found. Severe loss of hair cells and deterioration of the few remaining hair cells with loss of all sensory hairs was evident. In all sensory epithelia, an increasing number of supporting cells and ”cavities” inside the neuroepithelium were commonly found, with the cells sometimes standing in double rows. In the utricle and saccule, about half of the hair cells were remaining, and their luminal surface was covered by a single layer of smooth, flattened epithelial cells of hitherto unknown origin probably the collapsed macular roof.

Conclusion. The mix-mice display some specific morphological abnormalities. These are collapse of the membranous walls surrounding the sensory epithelia with a decreased endolymphatic space as a consequence. The intraepithelial cavities inside the sensory epithelia are a common finding. Similar changes have not been detected earlier. Loss of connective tissue centrally seems to be due to a loss of nerve fibers. The litter-mates showed herniations of the surface of the hair cells, degeneration of nerve chalices and disarray of sensory hairs. At present, they did not show a circling behavior. It could be possible that these animals turn into a circling behavior with increasing age and progression of the epithelial deterioration.

**BP1.5**

**Is the caloric stimulation of the vestibule hydrostatic or hydrodynamic in nature?**

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The mechanisms underlying caloric nystagmus are still a matter of debate. The original theory proposed by Barany and more recently by Pau and Limberg suggested that convective endolymphatic currents were involved. According to these authors the mechanism which leads to caloric stimulation of ampullar receptors is of hydrodynamic origin. However Gentine et al. suggested that the mechanism involved in caloric nystagmus is of hydrostatic rather than hydrodynamic origin.

In the present study the two models (hydrostatic and hydrodynamic) have been tested and compared to each other. The experiments, carried out in isolated labyrinth preparations of the frog, demonstrated that the predictions of the hydrostatic model were consistent with our results whereas those provided by the hydrodynamic one were not. Moreover, the transcupular pressure differences predicted

by the hydrostatic model of the semicircular canal were computed and compared to the patterns of neural activity recorded during thermal stimulation of ampullar receptors. The model was able to nicely reproduce all the features of the neural response. This strengthened the hypothesis that hydrostatic rather than hydrodynamic mechanisms are involved in ampullar receptors responses to caloric stimuli.

**BP1.6**

**Model based consideration of the caloric nystagmus from all canal-plugged monkeys**

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We found and reported that the caloric nystagmus could be elicited after plugging all six semicircular canals in monkeys. To understand the mechanism of this caloric nystagmus, we analyzed caloric nystagmus as a 3D eye-velocity vector and fitted a model.

Methods. Three cynomolgus monkeys were stimulated unilaterally with cold (20 103) water while upright, supine, prone, right-side down, and left-side down, before and after all six semicircular canals plugged. The decline in the slow phase velocity vector was determined over the last 37% of the nystagmus.

Results. Before plugging, yaw components varied with the convective flow of endolymph in the lateral canals in all head orientations. Plugging blocked endolymph flow, eliminating convection currents. Despite this, the caloric nystagmus was readily elicited, but the horizontal component was always toward the stimulated (ipsilateral) side, regardless of head position in regard to gravity. When upright, the slow phase velocity vector was close to the yaw and spatial vertical axes. Roll components became stronger in supine and prone positions, and vertical components were enhanced in side down positions. In each case, this brought the velocity vectors toward alignment with the spatial vertical. Consistent with principles governing the orientation of velocity storage, when the yaw component of the velocity vector was positive, the cross-coupled pitch or roll components brought the vector upward in space. Conversely, when yaw eye velocity vector was downward in the head coordinate frame, i. e. , negative, pitch and roll were downward in space. The data could not be modeled simply by a reduction in activity in the ipsilateral vestibular nerve, which would direct the velocity vector along the roll direction. Since there is no cross coupling from roll to yaw, velocity storage could not rotate the vector to fit the data. We postulated, therefore, that cooling had caused contraction of the endolymph in the plugged canals. This contraction would deflect the cupula toward the plug, simulating utriculofugal flow of endolymph. Inhibition and excitation induced by such cupula deflection fit the data well in the upright position but not in lateral or prone/supine conditions. Data fits in these positions required the addition of a spatially orientated, velocity storage component.

Conclusion. We conclude, therefore, that three factors produce cold caloric nystagmus after canal plugging: inhibition of activity in ampullary nerves, contraction of endolymph in the stimulated canals, and orientation of eye velocity to gravity through velocity storage. Although the response to convection currents dominates the normal response to caloric stimulation, velocity storage probably also contributes to the orientation of eye velocity.

**BP1.7**

**Effects of Intratympanic Gentamicin on the Vestibular Nerve**

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Intratympanic gentamicin injection has become an important form of treatment for intractable vertigo due to Ménière's disease. Single injections are often sufficient to control vertigo attacks, and we have shown that a single injection typically reduces the function of the patient's labyrinth as measured by the angular vestibulo-ocular reflex in response to rapid rotary head thrusts. The reduction in sensitivity, however, is not as severe as seen after surgical destruction of the labyrinth.

We hypothesized that some vestibular nerve afferent activity and vestibular sensitivity is preserved after a single injection of gentamicin. To test this hypothesis, we recorded extracellularly from vestibular afferents in chinchillas 2 weeks (n=9; early group) or 3 months (n=8; late group) after a single unilateral injection of gentamicin (26. 7 mg/ml) into the middle ear space. The spontaneous firing rate (± SD) was lower ($p<0.01$) on the treated side (47. 0 ± 23. 9 spikes/s in early group and 36. 3 ± 21. 2 spikes/s in late group) than on the untreated side (53. 7 ± 23. 6 spikes/s). The interspike intervals and coefficients of variation (CV) for spontaneous firing were distributed bimodally, with regularly- and irregularly-discharging afferent classes present on both the treated and untreated sides. The relative proportion of very regularly discharging afferents was increased after treatment with gentamicin.

Only 18% of the afferents on the treated side in the early group and 27% of those in the late group responded measurably to tilt or rotation. Tilt-sensitive afferents on the treated side had reduced sensitivities compared to those on the untreated side ($p<0.001$, 10. 4 ± 4. 3 vs. 44. 1 ± 28. 4 spikes/s/g in the early group, and 10. 7 ± 5. 1 vs. 34. 0 ± 15. 4 spikes/s/g in the late group). Rotation-sensitive afferents were likewise much less sensitive on the treated than untreated side ($p<0.001$, 0. 04 ± 0. 05 vs. 0. 34 ± 0. 35 spikes/s per °/s in the early group; 0. 03 ± 0. 02 vs. 0. 28 ± 0. 19 spikes/s per °/s in the late group). Sensitivity to externally applied galvanic currents was relatively unaffected by gentamicin treatment.

Intratympanic gentamicin ablates or markedly reduces the responses of vestibular afferents to vestibular stimuli. However, spontaneous firing is preserved, as are regular and irregular patterns of discharge and responses to electrical stimulation. The results suggest that the afferents themselves are minimally damaged after a single intratympanic application of gentamicin. Synaptic activity from partially damaged hair cells might explain the finding that both regular and irregular firing patterns persist despite loss of transducer function. (Supported by NIH R01

DC02390 and K23 DC00196)

**BP1.8**

**Intratympanic gentamicin effects on vestibular afferents**

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Gentamicin is toxic to vestibular hair cells, but the consequences of this hair cell toxicity on the physiology of vestibular-nerve afferents has not been previously been defined. To elucidate these effects, we recorded extracellularly from vestibular afferents in chinchillas 2 weeks (n=9; early group) or 3 months (n=8; late group) after a single unilateral injection of gentamicin (26. 7 mg/ml) into the middle ear space.

The spontaneous firing rate (± SD) was lower (p<0. 01) on the treated side (47. 0 ± 23. 9 spikes/s in early group and 36. 3 ± 21. 2 spikes/s in late group) than on the untreated side (53. 7 ± 23. 6 spikes/s). The interspike intervals and coefficients of variation (CV) for spontaneous firing were distributed bimodally, with regularly- and irregularly-discharging afferent classes present on both the treated and untreated sides.

Only 18% of the afferents on the treated side in the early group and 27% of those in the late group responded measurably to tilt or rotational stimuli. Tilt-sensitive afferents on the treated side had reduced sensitivities compared to those on the untreated side (p<0. 001, 10. 4 ± 4. 3 vs. 44. 1 ± 28. 4 spikes. s-1. g-1 in the early group, and 10. 7 ± 5. 1 vs. 34. 0 ± 15. 4 spikes. s-1. g-1 in the late group). Rotation-sensitive afferents were likewise much less sensitive on the treated than untreated side (p<0. 001, 0. 04 ± 0. 05 vs. 0. 34 ± 0. 35 in the early group; 0. 03 ± 0. 02 vs. 0. 28 ± 0. 19 spikes·s-1/deg·s-1 in the late group). Galvanic sensitivity, however, did not differ significantly between the sides.

Intratympanic gentamicin ablates or markedly reduces the responses of vestibular afferents to vestibular stimuli. However, spontaneous firing is preserved, as are regular and irregular patterns of discharge and responses to galvanic stimulation. The results suggest that the afferents themselves are minimally damaged in this early period after a single intratympanic application of gentamicin, and that some hair cells are preserved as well.

**BP1.9**

**Afferent responses to mechanical stimulation and drug application in mouse in vitro labyrinth**

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In a recently developed in vitro preparation of the mouse labyrinth we have recorded intra-axonally from anterior and horizontal primary afferents, close to the base of their respective cristae (<500 microns from hair cell/afferent synapse). We have mapped the position and background discharge rates of afferents to both cristae. Despite the trauma associated with isolation from the skull and lower recording temperatures (23 to 34 degrees C), bony labyrinths retain their ability to transduce mechanical stimulation into afferent discharge. Using a micropusher to indent exposed windows of membranous labyrinth we have characterised the response properties of both anterior and horizontal canal afferents. We studied afferent activity in response to sinusoidal indentations of the corresponding membranous canal and compared these results with those obtained by stimulating the adjacent canal.

In recordings from 97 afferents over a range of frequencies from 0. 01 to 10 Hz, afferents responded with sinusoidal changes in discharge rates and modulation of membrane potential in a predictable manner. Phase response of afferent discharge was characterised by frequency-dependent shifts in peak activity. Peak activity was always in advance of maximum indentation, with large phase leads at low frequencies (106 ± 28. 1 degrees for 0.01 Hz; mean ± s. d. ). The smallest phase leads occurred around 1 Hz; 15 ± 29. 3 degrees. These phase shifts are similar to those reported in in vivo recordings from mammals, despite our use of artificial rather than natural stimuli. Calculation of gain was more problematic, probably because indentation partially collapsed the canal. This made it difficult to provide consistent stimuli. Consequently while gain could be calculated for individual units these results could not be pooled across animals. This in vitro preparation also allows application of drugs and we have begun to study the effects of various neuromodulators on afferent discharge.

Our preliminary results suggest that TTX (1 μM) abolishes afferent discharge by acting directly on axons because its effect occurs within 30 seconds or less. CNQX (10 uM) can take up to 6 minutes to abolish background afferent activity suggesting that it probably acts at the hair cell / primary afferent synapse. Afferent activity was abolished much faster (< 60 seconds) after initial application and washout (10 mins) of CNQX, suggesting that the drug remains bound to receptors for some time. In conclusion, despite the drawbacks associated with gain calculations, isolated mouse in vitro labyrinths are viable preparations for studying transduction and synaptic mechanisms in the mammalian peripheral vestibular apparatus. (Supported by National Health and Medical Research Council of Australia, Garnett Passe and Rodney Williams Foundation, Hunter Medical Research Institute to AMB and RJC. )

**BP1.10**

**Development of Ion Channel Clusters and Synaptic Connections in the Bullfrog Saccule**

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During development, electrically resonant hair cells in the bullfrog saccule form ion channel clusters as well as afferent and efferent synaptic connections. To examine the temporal relationship between these events, we developed fluorescent probes for several ion channels, including a fluorescent derivative of charybdotoxin (Fl-CbTx), and verified by patch-clamp recordings that this toxin derivative retained its specificity for large-conductance Ca2+-activated potassium (BK) channels. Acutely dissected saccules were pre-treated for 10 mins with 1 mM gadolinium chloride to block the transduction channels of hair cells and subsequently labeled for 10-20 mins with Fl-

CbTx and a fluorescent dihydropyridine (Fl-DHP), which inhibited L-type Ca2+ channels, in low-calcium saline to prevent endocytotic uptake of the fluorescent probes. They were then rinsed, fixed for 1 hr with 4% paraformaldehyde, and immunolabeled with antisera against myosin VI, cytokeratin, or neurofilament proteins, which mark hair cells, supporting cells, and neuronal terminals, respectively. Using confocal microscopy and deconvolution, we then examined the development, distribution, and composition of ion channel clusters and the relationship of these ion channel clusters to neuronal terminals.

After incubation in Fl-CbTx and/or Fl-DHP, mature saccular hair cells displayed varying numbers of small puncta on their basolateral surfaces, indicating that they possessed both L-type Ca2+ and BK channels. These puncta, which ranged in size from <0. 25-1. 0 um, were co-localized with each other and were largely restricted to the basolateral region of mature hair cells. Ion channel clusters were closely associated with neuronal terminals, often forming a ring around the synaptic active zone. In contrast, developing hair cells on the saccular margins had larger numbers of small DHP-labeled puncta. These puncta were not co-localized with CbTx-labeled puncta, were not restricted to the basolateral region, and were found in smaller numbers around neuronal terminals. Supporting cells and neuronal terminals did not exhibit labeling with either probe.

We also are using multi-photon time-lapse microscopy to examine the dynamics of ion channel clustering in developing saccular hair cells in more detail. In these experiments, we are post-labeling saccular cultures with antisera against identified synaptic components to reveal which synaptic components are present before synapse formation and to determine if channel clustering precedes or follows neuronal innervation. (Research supported by NIH grants P30 DC04665 and DC02048 and NASA grant NAG2-1343. We thank T. Hasson of UCSD and J. Cyr of WVU for myosin VI and cytokeratin antisera. )

**BP1.11**

**Galvanic vestibular stimulation in the alert guinea pig: oculomotor, postural, and neural responses**

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Passing constant-current galvanic vestibular stimulation (GVS) over the surface of skin covering the mastoids in humans has previously been shown to induce ocular (e. g. MacDougall, 2000), postural (e. g. Coats & Stoltz, 1969), and perceptual responses. Our aim was to separately characterize ocular and postural responses induced during GVS delivered externally in the guinea pig as a step towards understanding responses in humans. We further sought to identify the primary vestibular neurons activated by external GVS in guinea pigs.

Five seconds of constant-current GVS was delivered through non-polarizing stainless-steel electrodes implanted bilaterally in each middle-ear tensor tympani muscle, external to inner ear perilymph. Bilateral stimulation (±30 microamp) was delivered between both electrodes, whereas unilateral stimulation (± 60microamp) was delivered between one electrode and a reference screw in the skull.

The three-dimensional eye positions of alert animals to these stimuli were recorded using the 3D dual search coil method with the head restrained 40 degrees nose down. Eye-movement recording was also obtained during surface GVS, which involved passing currents through disk electrodes positioned over locally anaesthetized skin behind each ear, corresponding to locations on the mastoid processes in humans. In a separate session, GVS-induced changes in the three-dimensional position of the unrestrained head were measured using Optotrak. In a further experiment, the GVS-induced responses of single primary vestibular afferent neurons were recorded extracellularly from anaesthetized animals using glass micro-pipette electrodes filled with 2M NaCl solution. Neurons were characterized by their natural sensitivity for static tilt and dynamic rotation of the head in all planes, and their galvanic threshold and sensitivity were assessed.

Eye movements induced by both surface and tensor-tympani GVS were predominantly tonic and vertical relative to the orbit of the eye within the roll plane of the head, with a small horizontal deviation, and no significant torsion. Eye movements were directed toward the anode and away from the cathode. The three-dimensional axis of induced eye rotation was not consistently aligned with known axes of any of the three semicircular canals (see Curthoys et al. , 1975). In alert, head-unrestrained animals, GVS induced changes in head posture: a lateral roll-tilt of the head directed toward the anode and away from the cathode. Maintained yaw head deviation directed toward the anode was also observed. No GVS-induced pitch of the head was observed.

Single-unit recordings revealed that GVS did not differentially activate any one vestibular sensory region: primary vestibular afferent neurons sensitive to either tilt or angular head rotation in any of three spatial planes had similar galvanic sensitivities. Hence, afferent neurons innervating all vestibular sensory regions (i. e. both otolith and SCC afferents) appear to be activated by externally applied galvanic stimulation. Moreover, the complementary signals generated were likely to have received central cancellation, e. g. between anterior and posterior SCC signals, resulting in the absence of pitch-plane eye and head deviation. Hence, combined roll- and horizontal-plane eye and head movements were induced, and are consistent with eye movements and lateral posture instability induced by surface GVS in human studies.

**BP1.12**

**Vibration-induced nystagmus in mice with unilateral vestibular dysfunction**

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Recently it has been shown that vibration stimuli could induce nystagmus in humans with unilateral dysfunction. We reported that vibration-induced nystagmus (VIN) could be frequently evoked in patients with severe canal dysfunction. It has been suggested that the generation of VIN could be strongly related to unilateral peripheral vestibular deficits. However, it was unclear what was stimulated by vibration and by what mechanism. We studied VIN in mice with unilateral vestibular dysfunction in order to explore these issues.

Materials and Methods. We prepared two kinds of

mice under general anesthesia by intramuscular injection of pentobarbital sodium (30 mg/kg body weight) and ketamine hydrochloride (40 mg/kg body weight). In some mice, a unilateral lateral semicircular canal was destroyed. And, in other mice, a unilateral posterior semicircular canal was destroyed. After the surgery they showed spontaneous nystagmus due to the destruction of semicircular canals. After the cessation of their spontaneous nystgmus, vibratory stimuli were presented. Vibratory stimulation was approximately 100Hz. Vibratory stimulation was presented on the skin on the bregma, the skin on the lambda, the mastoids, and the dorsal neck respectively. Nystagmus was observed and recorded using the video system.

Results. Nystagmus appeared as soon as vibratory stimulation was presented, while it disappeared as soon as the stimulation was stopped. VIN in mice with the destruction of the lateral semicircular canal was mainly horizontal while VIN in mice with the destruction of the posterior semicircular canal was mainly vertical-torsional.

Discussion. Asymmetry of the excitation between the healthy canal and the impaired canal by vibratory stimuli might cause VIN. Other factors might be involved to evoke VIN. Neck muscles might also play some parts in evoking VIN. The mechanism of VIN still remains to be clarified. However, experiments with animals such as mice may answer questions because we showed that mice also show VIN after unilateral vestibular dysfunction.

**BP1.13**

**Cranial nerve palsies: Herpes Simplex Virus Type-1 and Varizella-Zoster Virus latency**

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It is widely accepted that after primary infection HSV-1 and VZV ascend from the epithelial entry zone to the associated sensory ganglia by retrograde axonal transport. This means, e. g. from the sensory nerve endings in the oropharyngeal epithelia via chorda tympani to the geniculate ganglion (GG). Neighboring vestibular ganglia (VG) can be reached by further viral migration along the facio-vestibular anastomosis. From the VG the virus can spread to the spiral ganglia (SG) along several vestibulo-cochlear anastomoses. The plausibility of the latter route is supported by the distribution of HSV-1 found in these ganglia.

Reactivation of HSV-1 in the GG, VG, and SG is assumed to cause distinct and separate cranial nerve palsies, such as Bell's palsy or vestibular neuritis. In contrast to HSV-1 infection, reactivation of VZV in the GG usually causes a combined palsy of the facial and vestibulocochlear nerves (Ramsay Hunt syndrome, RHS). The following questions therefore arise with regards to the involvement of the vestibulocochlear nerve in RHS: is it due (1) to concomitant infection in all three temporal bone ganglia, (2) to a co-reactivation of HSV-1 in the VG and SG? or, (3) to an extension of the inflammation from the GG to the neighboring vestibular and cochlear nerves? The frequency of VZV latency has so far been tested for only single ganglia in different individuals. Therefore, it is reasonable to test the distribution and association of both viruses in the three ganglia of the same individual.

Temporal bones from ten individuals were obtained from the Institute of Forensic Medicine at the time of autopsy (5 females; ages 4 months - 58 yrs). The GG, VG, and SG were tested using a multiplex nested PCR assay for HSV-1 and VZV infection.

A dual infection with HSV-1 and VZV was detected in four individuals. Three of them had a double infection in the GG and one a double infection in the VG. VZV latency without HSV-1 infection was found in the GG, VG, and SG of only one individual. HSV-1 DNA was detected more frequently (seven individuals). The exceptional VZV infection of one VG without involvement of the GG is compatible with a hematogenous spread.

Our data are not conclusive enough to clearly answer the initial three questions. However, the detection of VZV predominantly in the GG without concomitant involvement of the other ganglia do not support the view that the multiple nerve involvement in RHS is caused by reactivation of VZV in these ganglia. The frequent association of VZV infection and HSV-1 infection in the GG theoretically makes it possible that VZV reactivation in GG induces a reactivation of latent HSV-1 in the VG and SG. However, the most likely explanation is the that inflammation spreads from the GG towards the neighboring ganglia or directly to the labyrinth and the cochlea, since it is known that VZV infection triggers a strong inflammatory response that affects adjacent tissue and vascular structures.

**BP1.14**

**Anterior canal failure causes ocular torsion without perceptual tilt due to intact otolith function**

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Healthy subjects are able to adjust their subjective visual vertical (SVV) within a precision of ±2. 5 degs when placed in front of an unstructured background providing no cues for visual orientation. This ability is attributed to the vestibular system (namely the otolith organs) and to some extent also to the somatosensory system. A direction-specific tilt of the SVV is a typical and sensitive sign of peripheral and central vestibular disorders. Vestibular disorders with a vestibular tone imbalance in roll plane not only involve a tilt of SVV but also an associated ocular torsion (OT) and the tilt of SVV increases with larger angles of OT, both in the same direction. This raises the following questions: (1) Are the tilts of SVV and OT two independent signs of a common vestibular tone imbalance or is the tilt of the SVV the perceptual correlate of the OT? (2) What are the differential effects of isolated vertical SCC and otolith dysfunction on both signs? These questions can neither be examined in animal experiments (determination of SVV is not possible) nor in subjects with lesions of the eighth nerve (which affect both otolith and canal function simultaneously).

A patient with anterior semicircular canal (aSCC) dehiscence syndrome underwent surgical patching that caused an isolated dysfunction of the left aSCC postoperatively (gain of the plane-specific VOR = 0. 43). He exhibited significant OT toward the side of the affected labyrinth (17 degs excyclotropia of the ipsilateral eye), but no displacement of the SVV. The patient posed an

intriguing puzzle: binocular torsion of the eyes was not associated with a tilt of the SVV. This finding suggests that the ocular motor and perceptual system in the roll plane may operate independently under exceptional conditions.

The case is unique in that dysfunction of the aSCC is isolated and the receptors of the labyrinth that indicate the direction of gravity (the otolith organs) are not affected. In other words, torsion of the eyes was caused by an inappropriate canal input. Verticality relies on appropriate otolith input. Thus, an intra-sensory vestibular mismatch occurs between the canal and otolith signals (SCC indicating self-rotation in the plane of the affected canal vs. otolith indicating true verticality). This mismatch is resolved differentially for ocular motor function and perception. There is also an inter-sensory mismatch between the visual and vestibular signals (rotation of the retina vs. true perceived verticality). The adjustment of the SVV was, nevertheless, correct despite constant rotation of the retina. At least two causative mechanisms are conceivable: (1) central adaptation to the inappropriate OT occurred by virtue of the visual input within the 5 post-operative days and/or (2) a space constancy mechanism used an efference copy of the ocular motor signal. This exceptional case has clinical and experimental implications, particularly for the modeling of ocular motor and perceptual function.

Current mathematical models of otolith-canal and visual-vestibular interaction must also be revised, for they assume that an ocular motor and perceptual response use the same neuronal structures and are directly linked.

**BP1.15**

**Potassium channel blocker 3,4-diaminopyridine improves severe head-shaking nystagmus**

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Head-shaking nystagmus (HSN) generally indicates a peripheral tone imbalance of the vestibulo-ocular reflex (VOR), which can be caused, for instance, by semicircular canal paresis. During a head-shaking maneuver, the ipsilateral dynamic VOR deficit leads to an asymmetric accumulation within the velocity storage. The discharge of this velocity determines the direction of HSN, usually toward the unaffected ear.

We report on a 55-year-old patient who had recurrent, severe episodes of vertigo and oscillopsia for 1⁄ years. These episodes could be reproduced by rapid changes in horizontal head position and head-shaking. The patient also had a slowly progressive hypacusis and intermittent tinnitus of the right ear.

A head-shaking maneuver in the horizontal plane induced a horizontal-counterclockwise rotatory nystagmus toward the left. This was accompanied by oscillopsia and a tendency to fall to the right. After the head-shaking maneuver had been repeated five times, scleral-coil recording revealed that the peak-slow phase velocity (PSPV) of the horizontal component was 70 degs/s. Up and down head-shaking as well as head-shaking in the planes of the vertical canals did not induce vertigo or nystagmus. Cranial MRI showed a neurovascular cross-compression of the right eighth nerve in the root-entry zone of the anterior inferior cerebellar artery (AICA). Auditory evoked potentials showed that in the right ear waves I and II were reduced and wave III was prolonged.

Assuming a pathological excitation of the eighth nerve by neurovascular cross-compression ("ephaptic" interaxonal transmission of action potentials), as also occurs in vestibular paroxysmia, we first treated the patient with carbamazepine (200 mg/d), which worsened his signs and symptoms. Subsequently, he was given the potassium channel (A-current) blocker 3,4-diaminopyridine (3,4-DAP; 3 x 15 mg/d), which considerably improved the signs and symptoms. Eye-movement recordings documented this improvement as a reduction of the PSPV of the horizontal component of the HSN from 70 degs/s to 20 deg/s. In parallel, body sway, which was measured by posturography, also significantly improved during the head-shaking maneuver.

On the basis of the direction of the nystagmus, the MRI findings, and the effects of 3,4-DAP, we conclude that the HSN of this patient was caused by a transient hypofunction of the right eighth nerve due to mechanical compression by the AICA. This in turn led to a transient, partial conduction block. The potassium channel blocker 3,4-DAP improved the symptoms by blocking the A-current and thereby prolonging the duration of action potentials and improving their conduction.

**BP1.16**

**Effective immunosuppressive therapy in a patient with bilateral vestibulopathy and antibodies against inner ear structures**

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Some types of bilateral vestibulopathy seem to arise from systemic autoimmune processes, for example, lupus erythematosus, polychondritis, Cogan's syndrome, or rheumatoid arthritis. About 20% of bilateral vestibulopathies remain idiopathic despite extensive diagnostic workup. We previously demonstrated antilabyrinthine antibodies in the serum of eight of 12 patients with "idiopathic" bilateral vestibulopathy (Arbusow et al. , 1998). Although the pathogenicity of these antibodies remains unclear, their appearance seems to indicate organ-specific immune dysregulation. Here we report on a patient with bilateral vestibulopathy who recovered after immunosuppressive steroid therapy. The recovery correlated with a disappearance of serum autoantibodies against inner ear structures.

In 1995 a 55-year-old man was admitted to the hospital with sudden attacks of rotational vertigo, lasting for 30-60 seconds. Caloric irrigation (44°C) showed a reduced maximum slow phase velocity of horizontal nystagmus of 6°/s on both sides. Serum autoantibodies against the inner ear structures, the cochlea and the vestibular organ, were positive (>1:100). Assuming an immune dysregulation as the cause of the bilateral vestibular dysfunction, we treated the patient with glucocorticoids for 6 weeks, beginning with 100 mg/day methylprednisolone. A follow-up examination after the end of the therapy showed improvement of vestibular function on both sides with a slow phase velocity of 14°/s after caloric irrigation (44°C). Serum autoantibodies remained positive. In 2002 the patient was seen for another follow-up examination 6 years after the immunosuppressive steroid therapy. Caloric vestibular testing showed a complete

recovery of vestibular function with a maximum slow phase velocity of 25°/s (44°C) on both sides. Serum autoantibodies against the cochlea and the vestibular organ had disappeared.

Some of the so-called idiopathic vestibulopathies may be due to autoimmune inner ear disorders. Immunosuppressive steroid therapy may have a delayed therapeutic effect in patients with incomplete, autoimmune-induced bilateral vestibulopathy. Therefore, we recommend determining inner ear autoantibodies in such cases, since incomplete autoimmune bilateral vestibulopathy may be responsive to immunosuppressive therapy.

Arbusow V, Strupp M, Dieterich M, Stöcker W, Naumann A, Schulz P, Brandt T (1998) Serum antibodies against membraneous labyrinth in patients with "idiopathic" bilateral vestibulopathy. J Neurol 245:132-136

**BP1.17**

**Congenital inner ear malformation without sensorineural hearing loss**

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Generally, inner ear malformations are associated with sensorineural hearing loss. However, there are several reports of the inner ear deformity with normal hearing. The present case had dysplasia of the lateral and posterior semicircular canals (LSCC, PSCC) in both ears with normal hearing. High resolution computed tomography (CT) and magnetic resonant imaging (MRI) enabled a precise diagnosis of the deformed lesion. We herein present the results of the vestibular tests in comparison with the radiological findings.

Case report : A 37-year-old woman complaining of dizziness and disequiliblium while walking came to our clinic on Dec. 10th 2000. She experienced oscillopsia while walking and tended to deviate to the left side. Pure tone audiometry, stabilography and auditory brainstem response showed no definite abnormalities. On stepping test, she staggered and slightly deviated to the left but the total length and the angle were within the normal range. The voluntary eye movement was full. The horizontal vestibulo-occular reflex was present. No nystagmus was observed in the tests including gaze, positional and positioning tests. She complained of uncomfortable sensation by changing the pressure to her left ear without nystagmus. The OKN and ETT showed normal response. The caloric stimulation with 20ml of ice water elicited no nystagmus in the left ear and reduced response in the right ear. The vestibular evoked myogenic potential (VEMP) was normal in the right ear. In the left ear, the P13 wave latency was prolonged and P13-N23 interval was shortened. High resolution CT showed hypogenesis of the bonny labyrinth in both ears. Bilateral PSCC and LSCC dysplasia and dilatation of the vestibular were detected. Left cochlea appeared dysplastic, but the right cochlea had a normal shape. In MRI, signal intensity of the bilateral cochlea was slightly decreased. The bilateral superior semicircular canals (SSCC) were normal. Bilateral LSCC were not well delineated. Both PSCC were not detected.

Discussion. According to the phylogenetic study, SSCC is the first to form, followed by PSCC and then LSCC. For this reason, LSCC may be particularly vulnerable and frequently malformed. It is unusual that the deformity of PSCC was severer than LSCC as observed in our case. Those three canals are formed during the fourth to seventh embryonal periods. Any insult during this period might have blocked the growth process, but real cause remains unclear. Regarding the hearing level, Komune et al reported bilateral Mondini Dysplasia with normal hearing. Jacob also reported three cases of LSCC malformation with normal hearing. In those cases, the deformity might be limited to the vestibular system. Regarding the vestibular function, Valvassori reported a case of normal vestibular function with LSCC hypoplasia and stressed the inner ear abnormality does not necessarily indicate a vestibular dysfunction. In the present case, the dizziness might be caused by the unknown reduction of her left peripheral vestibular function.

**BP1.18**

**Acute Otolithic and Semi-circular Canals Deficits After Whiplash Injuries**

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Whiplash injuries correspond to an acceleration-deceleration mechanism of energy transfer to the neck. The most common causes are car accidents such as rear-end, frontal or lateral collisions. Such mechanisms might generate bony and/or soft-tissue injuries.

Three patients suffering from acute peripheral vestibular dysfunction several minutes to hours after a car collision with whiplash injury, without head trauma are reported. There was 1 man and 2 women aged 57, 22 and 56 years, respectively. All were seat-belted drivers. The accident was a frontal collision in one case, a rear impact in the second and lateral in the third. All patients complained immediately after the accident of cervicalgia, headache, acute vertigo with erroneous body movements and slipping of image with head movements. One patient described a sudden tilt of the environment to the left when driving. Another patient reported tinnitus and hyperacusis in both ears during the hours immediately following the accident. The complaints were recurrent more than one year after the accident in one patient. The otoneurological findings showed bilateral canalolithiasis in one patient and an acute peripheral vestibular deficit in two patients. Tilt of the subjective visual vertical was measureed in all patients. Cerebral MRI was normal.

As angular and linear accelerometers, the vestibular organs are directly exposed to high forces generated by whiplash mechanisms. Vertigo generated by peripheral vestibular lesions is probably underestimated in whiplash injuries and may often be incorrectly attributed to cervical or cerebral lesions. A quick identification of peripheral vestibular disorders after whiplash mechanisms might provide an opportunity for appropriate treatment and document the correlation between the accident and the complaints in case of later judicial conflict.

**BP1.19**

**Vestibular evoked myogenic potentials in neurofibromatosis type 2**

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Objective. Neurofibromatosis type 2 (NF2) is characterized by bilateral vestibular neurofibromas. However, which division of the vestibular nerve affected remains unexplored. This paper attempts to assess whether NF2 is originated from the superior or inferior vestibular nerve before surgery.

Methods. A total of seven NF2 patients (two men and five women) underwent pure-tone audiometry, caloric test, vestibular evoked myogenic potential (VEMP) test, and MRI examination.

Results. Audiometry revealed mean hearing level less than 26 dB for 1 ear, 26-70 dB for 8 ears, 71-90 dB for 3 ears, and more than 90 dB for 2 ears. Caloric test revealed absent response in 71% of the fourteen ears. Seven ears underwent VEMP test, and only one (14 %) displayed absent VEMPs. MRI depicted space-occupying lesions in bilateral auditory canals, including small- sized tumor in three ears, medium-sized in seven ears, and large-sized in four ears. The tumor size of NF2 is related to the caloric response, but unrelated to the mean hearing level or VEMPs.

Conclusion. NF2 originates from the superior vestibular nerve more than the inferior vestibular nerve. It prefers to invade the cochlear nerve rather than the inferior vestibular nerve.

**BP1.20**

**Aural pressure treatment for Menière's disease**

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On the treatment scale for Menière's disease, there is a place for pressure treatment. Pressure chambers have been used for acute attacks and for patients in periods of active disease. Local pressure in the ear has been used and evaluated by pure tone audiometry and electrocochleography before and after treatment, all in the same day. Significant improvements were found.

In a two-week study fifty-six patients with active Menière's disease were evaluated. Half of them were treated using local pressure in the ear and half of them used a placebo-apparatus with the same instructions five minutes three times daily. The active machine (Meniett) gave pressure pulses for five minutes at presssure amplitudes of 12 cm water. All patients had a grommet in the tympanic membrane inserted two weeks before treatment. Questionnaires using visual analog scales showed significant improvements concerning vertigo, tinnitus and aural fullness for the Meniett patients and no improvement in the others. For the low frequencies, audiometry showed a significant improvement and in electrocochleography for the Meniett treated ears and not in the placebo ears.

Before a shunt operation or gentamicin treatment, pressure treatment should be tried as it seems to be an easy, safe and often effective method of treatment.

**BP2.1**

**Predicting the Meniere's course using vestibular evoked myogenic potentials**

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Objective. Staging of Meniere's disease proposed by AAO-HNS (1995) was based on the arithmetic mean of the pure tone thresholds at 0. 5, 1, 2, and 3kHz. Accordingly, stage I means pure tone average less than 26 dB; stage II, 26-40 dB, stage III, 41-70 dB, and stage IV, more than 70 dB. Since saccule, next to cochlea, is the second most frequent site for hydrops formation, whether vestibular evoked myogenic potential (VEMP) response can reflect the Meniere's course remains unexplored.

Methods. Forty patients (23 men and 17 women) with unilateral definite Meniere's disease were enrolled in this study. The latencies of p13 and n23, amplitude p13-n23, and the interaural amplitude difference (IAD) over the sum of amplitudes of both ears was measured, and correlated with the duration, and mean hearing level.

Results: Six ears were classified as stage I, including normal VEMPs in 5, and augmented VEMPs in 1, with the mean IAD ratio -0. 02 + 0. 20. In 12 ears of stage II, which consisted of normal VEMPs in 7, augmented VEMPs in 2, depressed VEMPs in 1, and absent VEMPs in 2, with the mean IAD ratio -0. 12 + 0. 39. Stage III was noted in 17 ears, including normal VEMPs in 10, depressed VEMPs in 4, and absent VEMPs in 3, with the mean IAD ratio -0. 30 + 0. 30 . Stage IV was in 5 ears, including normal VEMPs in 2, absent VEMPs in 2, and depressed VEMPs in 1, with the mean IAD ratio -0. 54 + 0. 43. Comparing the IAD ratio among ears of four stages demonstrates a significant difference ($p<0.05$, ANOVA test).

Conclusions. The IAD ratio of VEMPs could be useful to predict the course of Meniere's disease.

**BP2.2**

**Management of bilateral Meniere's disease using low pressure pulses**

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Patients with Meniere's disease affecting both ears often pose difficult clinical problems. Failure of medical treatment leaves limited therapeutic options for this group of patients. Low pressure pulse technology is a non destructive method that has been shown to control symptoms in intractable Meniere's disease. Effects of Meniett treatment are presented in a number of patients with definite Meniere's disease with bilateral affection.

Material and Methods. Fourteen patients with definite Meniere's disease affecting both ears were included. Age 40-78 (mean 60) who all failed medical therapy. All patients having acute vertigo spells prior to treatment. Eight patients were suffering from a bilateral hearing impairment ( > 65 dB). Evaluation of vertigo spells and hearing function were made using the AAO-HNS criteria. The average duration of symptoms prior to treatment was 5 years. The follow up time during treatment was from 2 to 4 years.

Results. Ten patients were relieved from definite spells of vertigo. Two reported a significant decrease in the number of spells. Imbalance persisted in older patients. There was no significant improvement in hearing levels in the patients as a group. Patients classified as 2 and 3 AAO-

HNS showed improvement in hearing levels.

Conclusions. The low pressure pulse treatment seems an appropriate treatment in patients with active inner ear symptoms who face either continuous functional disability or uncertainties of an invasive intervention.

**BP2.3**

**The Use of Transtympanic Electrocochleography in the Diagnosis of Meniere's Disease**

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Since 1990, over 4000 patients have been evaluated using trans tympanic electrocochleography. There have been no serious complications and no persistent perforations. The main clinical indication has been to detect an abnormal summating potential as an indicator of endolymphatic hydrops and to aid the diagnosis of Meniere's disease. 1050 ears have been tested who were diagnosed to have definite Meniere's disease according to the AAOOHNS criteria. These Meniere's ears were compared with normal ears and the ears of patients who had a hearing loss but were not suspected as having Meniere's disease.

It was found that tone burst recordings gave a better indication of the presence of an abnormal SP than click recordings. The 1kHz SP appeared optimal.

The data has been analysed for each hearing level and diagnostic levels ste at 2 standard deviations from the normal data. An abnormal click SP/AP ratio ( 100dBHL) was an ratio of over 50%. The abnormal 1kHz SP (100dBHL) was an SP more negative than -6uV.

| | Click SP/AP | 1kHz SP |
|---|---|---|
| Diagnosis rates | Over 50% | more negative than -6uV |
| Hearing loss 0-35dBHL | 12% | 24% |
| Hearing loss 40-65dBHL | 38% | 73% |
| Hearing loss 0ver 70dBHL | 52% | 2% |

It is concluded that trans tympanic EcochG can be a useful adjunct to the clinical diagnosis of Menière's disease.

**BP2.4**

**Saliva melatonin in patients with Meniere's disease**

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The pathological mechanism of Meniere's disease is an endolymphatic hydrops, however the cause of the disease is not necessarily clear. It has been expected that stress participates in development of symptoms of Meniere's disease, and stress hormone such as vasopressin may be participating in formation of the endolymphatic hydrops. A secretion of the hormone has been known to have a circadian rhythm, of which the key neuroendocrine modulator is melatonin; pineal hormone. However, there are few studies on 'melatonin' in Meniere's disease.

Methods & Materials. Saliva samples were collected from 14 patients with Meniere's disease to measure the melatonin concentrations in morning by radioimmunoassay, and in 7 of them extracted their saliva were extracted every four hours a day to estimate circadian rhythm parameters by single cosinor analysis. In addition, the relevance of the degree of stress by a questionnaire of an environmental stress was investigated. Same Eight patients with sudden deafness and eight age-matched healthy subjects

Results. Saliva melatonin concentrations of the Meniere's disease patients in morning were significantly lower than control. Moreover, average stress score in Meniere's disease group was 8. 5+-3. 9 points and significantly higher than 3. 5+-5. 1 points in control group ($p< 0. 01$). The melatonin concentration to the protein concentration in saliva of Meniere's disease group is 0. 5+-0. 7 pg/mg. It was significant lower value than melatonin concentration of saliva (2. 5+-2. 0 pg/mg) in the control group. No significant difference in the sudden deafness group (2. 6+- 3. 7 pg/mg) was shown. However, there was no significant correlation between the saliva melatonin concentration and the stress score. Saliva mealtonin concentration of Meniere's disease patients was not correlated with their hearing threshold level, Canal paresis % in a caloric test and the vertigo spells. In circadian rhythm of saliva melatonin, an intersubject variation of acrophases in Meniere's disease group was significantly larger and its amplitude was significantly smaller, compared with control.

Discussion. The present result suggest that hyposecretion of melatonin and change of melatonin rhythm could influence the development of Meniere's disease, however it remains to be opened how hyposerection of melatonin influences the formation of endolymphatic hydrops. ( This research is supported by a grant-in-aid from the Japan Society for the promotion science (No. 11770986) and a grant-in-aid from Gifu University School of Medicine for the promotion of science. )

**BP2.5**

**The Semicircular Canal Implants**

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We have developed a neural prosthesis, which is intended to reproduce the function of semicircular canals in patients with bilateral vestibular end organ failure or chronic vertigo. This novel device consists of a spatial status detector, radius detector, an integrated circuit and nano-electric arrays. The detectors are implanted in the mastoid antrum so that head movement produces forces in the detector, which simulate those normally applied on the semicircular canals. Detectors contribute data for computation of the parameters for stimulation of vestibular nerve endings at each of the semicircular canal ampullae. The spatial status detector is a centrally suspended insulated surgical steel disc, with two contact points at its periphery, moving freely within a hollow glass sphere lined from inside with titanium matrix grid. Along with the head-movement, the insulated surgical steel disc moves in relation to the intersections of the matrix grid. Transfer and transit time between the intersections of the matrix grid are used to detect the position of the disc in relation to the sphere. These parameters are utilized to navigate the position of the poles at the ends of the disc in order to determine the spatial position of the head and to determine the change in the angle for the period of head rotation. The radius detector is a conventional piezo electric linear acceleration detector, mounted on the moving disc. The

later contributes the data for the computation of the radius of the curved path of head.

Using the above parameters the processor determines the frequency of neuronal stimulation for that specific tilt episode and forwards that to stimulator. The stimulator provides this information to the nano electric arrays in form of frequency modulated biphasic square wave pulses. The nano-electric arrays are made from platinum discs of one square micrometer area embedded in the biocompatible material and fixed near the ampullae of the respective semicircular canals. The nano-electric array transmits the information to the vestibular nerve. There are also recording electrodes, scattered in the group of the stimulator arrays; the function of which is to monitor the activity of the vestibular nerve and providing the feedback signals to the integrated circuit.

The sensors are kept in the mastoid antrum in vicinity of the semicircular canals. The integrated circuit and the secondary coils under the dura of the squamous part of the temporal bone and the cables coated with the biocompatible material are to be buried in a nick made in the temporal bone beneath the dura. The device is energized with enveloped electrical waves. This enables to reprogram the integrated circuit after implantation and tune up the device as per the patient's adaptation.

In basic terms, this device will be helpful to the patients with chronic vertigo to minimize their spells of giddiness and will imitate the vestibular functions in the patients with bilateral nonfunctioning labyrinth. The device sensor is also intended to use for navigating the limb movements and using this information in functional neuronal stimulation in patients with movement disorders.

**BP2.6**

**Oculomotor Findings Mimicking Central Disorders in Severe Meniere's Disease**

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Objective. Patients with severe Meniere's disease face problems with balance even during attack free periods, and many of them also have problems of visual targeting on objects. The aim of the present study was to study association of these symptoms with oculomotor findings and to study the degree of oculomotor pathology in severe Meniere's disease.

Methods. Twenty-six patients with severe Meniere's disease were examined. Pseudo-random saccades and pseudo-random pursuit eye movements (PEMs) were tested at the same time, before or after gentamicin treatment of the affected ear. For normative data, voluntary eye movements in 45 control subjects were tested. Severity of symptoms in Meniere patients was assessed according to the Total Handicap Score of AAO-HNSF (1985).

Results. Saccadic eye movements and PEMs were deteriorated in patients with Meniere's disease. The oculomotor dysfunction mainly composed of prolongation of latency in saccades or reduction of gain in PEMs. The latter disorder was due to saccadization of PEMs. Phase lag of PEMs was not affected, as saccades compensated the total eye tracking. Severity of symptoms in Meniere patients correlated with prolongation of latencies and reduced ipsilateral peak velocity in saccades and with poorer gains in PEMs.

Conclusion. The oculomotor dysfunction found in this study can be best interpreted as a timing error of saccades and PEMs in patients with severe Meniere's disease. Misleading information derived from the affected vestibular system may disturb the assessment of location data, but the present results indicate that even timing of the oculomotor performance was disturbed. The results support the idea that a severe non-predictable vestibular disorder may cause a prolongation of premotor processing of voluntary eye movements resulting in increased latency of saccades and saccadization of PEMs.

**BP2.7**

**A Novel Treatment Modality with Reference to Eustachian Tube Function in Meniere's Disease Patients**

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Clinical reports on whether ear fullness in patients with Meniere's disease is due to tubal dysfunction or related to endolymphatic hydrops are few and far between. In the present study, Eustachian tube function (ETF) was examined to clarify the origin of ear fullness for effective treatment planning in patients with Meniere's disease.

Methods. Thirteen patients with relatively intractable Meniere's disease and complaining of moderate or severe ear fullness had their ETF examined by sonotubometry, tubal catheter insufflating test, and tubo-tympanum-aerodynamography. Diagnosis of tubal dysfunction were made when two out of the three tubal function tests had the same results.

Results. Unexpectedly, 9 of 13 examined patients (69%) proved to have patuolous eustachian tube (PET) while 2 had tubal stenosis and 2 showed a normal Eustachian tube function. The nine patients with PET including 6 who have persistent vertigo despite standard medical treatment were treated by a vasodilator (dipyridamole: 75 mg/day for 6 months) or/and an anti-hypotensive drugs (midodrinehydrochloride: 4mg/day for 6 months), to assess the efficacy of PET therapy in the control of vertigo in Meniere's disease. Interestingly, complete relief of vertigo and ear fullness was obtained and maintained for more than 6 months in 4 of the 6 intractable patients, indicating that Eustachian tube dysfunction may be one of the essential factors involved in the development of ear fullness in patients with Meniere's disease.

This observation further suggests that alleviating the abnormally patent Eustachian tube by either a vasodilator or an anti-hypotensive drug might be an important step in the control of both persistent vertigo and steady ear fullness in this pathological entity.

**BP2.8**

**Otolith Dysfunction During Vertiginous Attacks of Meniere's Disease**

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In vertiginous attacks of Meniere's disease there are various types of vertigo: rotatory vertigo, dizziness and drop attack. The sites of lesions in the vestibular organ in Meniere's disease are not the same among individuals or from one attack to another. When a patient complains of dizziness without spontaneous nystagmus, otolith dysfunction cannot be ruled out. The purpose of this study was to evaluate otolith dysfunction during vertiginous attacks of Meniere's disease and delayed endolymphatic hydrops (DHE).

Material and Methods. Vestibular function tests were carried out daily for more than 5 days on 11 patients during vertiginous attacks (Meniere's disease 9, DHE 2). Ataxia was evaluated by a stepping test with eyes closed. Semicircular canal dysfunction was evaluated by positional nystagmus (spontaneous nystagmus) observed by means of an infrared video camera. Otolith dysfunction was evaluated by ocular torsion (OT) in the sitting position. OT was obtained on a fundus photograph taken by a scanning laser ophthalmoscope (Rodenstock). In the present study we defined otolith dysfunction as an abnormal change of OT without spontaneous nystagmus and also as an abnormal change of OT without a change of spontaneous nystagmus. The angle was measured by projecting a straight line through the center of the pupils and fovea against a horizontal line as a base. In the right eye counterclockwise rotation from the perspective of the examiner was defined as positive excyclotropia, while in the left eye clockwise rotation was defined as positive. Measurements were taken twice and averaged, and OT ([right eye OT / 2 - left eye OT / 2]) was calculated. From data on 53 normal subjects the abnormal range of OT was seen to be over 5. 0 degrees and the abnormal change of OT was seen to be over 2. 5 degrees between the 2 measurements.

Results. While we found ataxia as a result of stepping test, 6 of the 11 patients showed spontaneous nystagmus while 6 of the 11 patients showed an abnormal change of OT. In the 6 patients with spontaneous nystagmus, 2 showed an abnormal change of OT, the direction of which was opposite to the direction of spontaneous nystagmus, and 4 showed no change of OT. In the 5 patients without spontaneous nystagmus, 4 showed an abnormal change of OT and one showed no change of OT in spite of suffering from ataxia. In 2 patients this change persisted for over half a year. Drop attack was recognized in 2 of 5 patients without spontaneous nystagmus.

Conclusion. We found that vertiginous attacks of Meniere's disease and DHE can be caused by semicircular canal dysfunction or by otolith dysfunction alone. However, it is unclear whether vertiginous attacks are caused by both semicircular canal and otolith dysfunction, or by both lateral semicircular canal and vertical semicircular canal dysfunction when the abnormal change of OT and spontaneous nystagmus synchronize, because OT may reflect not only otolith function but also vertical semicircular canal function.

**BP2.9**

**Prism Spectacles as a Brace for Vestibular Asymmetry. (Study of the effect of weak prismatic spectacles on unilateral Ménière's disease patients)**

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Over the past 60 years a small number of MDs in the Netherlands have been prescribing specific weak asymmetric prism spectacles for Ménière patients to relieve vertigo symptoms and to reduce the frequency and severity of attacks according to the guidelines described by G. P. Utermöhlen in 1941

Methods. This is a retrospective cohort study of long term improvement based on subjective self-reports by patients with unilateral Ménière's disease who have been treated by weak asymmetric base-in prisms, and whose medical records have been on file. The power of the prisms was directed by a walking test using an after-image. Patients were required to walk towards an earth-fixed light source placed straight ahead which causes an afterimage. With the afterimage patients had to walk back- and forth in the dark; a "Marche-en-etoile" followed. Without prisms, the walking pattern typically deviates to the side of the most impaired vestibulum. With addition of the correct prisms, walking changed to a linear pattern. The self-ratings were analyzed in relation to both vestibular and ophthalmologic factors.

Findings. The preliminary results show that more than 90% of the patients benefited from the treatment. Success was even greater when the affected side as diagnosed by an ENT specialist coincided with the deviation direction in the walking test, when the difference in heterophoria between far and near fixation was large, or when patients fell both categories. The greatest subjective improvement was achieved in patients with a convergence insufficiency of at least 4 diopters.

Interpretation. Vestibular information, whether it be correct or not, may be used for egocentric spatial orientation, including navigation through space. Irrespective of a possible explanation, treatment of Ménière s disease with specific prism glasses is at least as effective as other therapies. The effect appears to be related to the severity of a particular vergence oculomotor dysfunction. It has the advantages of being low cost, simple in its application, non-invasive, without any harmful risks, and is likely to have as high a degree of acceptance. This method should be considered before chemical or surgical ablation.

**BP3.1**

**Vertical canal function in normal subjects and patients with benign paroxysmal positional vertigo**

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We developed a new rotational test to evaluate the function of the vertical semicircular canal (VSCC). The subjects sat on the rotating chair, which was designed to stimulate the VSCCs, with the head, neck and back tilted 60 deg backward and the head rotated 45°to the right or left side from the sagittal plane. Consequently, the pair of right anterior semicircular canal (ASCC) and left posterior semicircular canal (PSCC) or that of the left ASCC and right PSCC were brought into a plane perpendicular to the rotational axis of the chair. When Ss were rotated

sinusoidally at 0. 1, 0. 3, 0. 5, 0. 7 and 1. 0 Hz with a maximum angular velocity of 50 deg/sec, the pair of VSCCs was periodically stimulated.

Eye movements induced by the stimulation of VSCC seem to consist of vertical and torsional components. In order to evaluate the exact gain of VSCC-ocular reflex, slow phase eye velocity (SPEV) around the axis of eye rotation induced by the stimulation of VSCC had to be measured. For this purpose, we used our technique for analyzing the rotation vector of tridimensional eye movements with infrared CCD camera (Imai, et al. , 1999). The gain of VSCC-ocular reflex was calculated as the ratio of SPEV around the axis of eye rotation to head velocity.

In normal subjects, the mean gain of right PSCC was 0. 50 at 0. 1Hz, 0. 56 at 0. 3 Hz, 0. 61 at 0. 5Hz, 0. 69 at 0. 7Hz and 0. 82 at 1. 0Hz. The mean gain of other three VSCC-ocular reflexes was almost of the same value at all frequencies.

We then measured the gain of PSCC-ocular reflex in patients with benign paroxysmal positional vertigo (BPPV). According to the canalolithiasis hypothesis of BPPV, nystagmus was induced by canalolithiasis of the PSCC of the undermost ear in positional vertigo. In patients with suspected canalolithiasis in the right PSCC, the mean gain of right PSCC-ocular reflex was 0. 45 at 0. 1 Hz, 0. 58 at 0. 3Hz, 0. 64 at 0. 5Hz, 0. 73 at 0. 7Hz and 0. 83 at 1. 0Hz. The mean gain of left PSCC-ocular reflex in patients with suspected canalolithiasis in the left PSCC was almost of the same value, and not significantly different from that of normal subjects at all frequencies. These findings indicate that the function of PSCC in patients with BPPV was not affected. They further suggest that canalolithiasis in PSCC causes additional endolymphatic flow in response to gravity, but not during rotational stimulation, because the acceleration acting on canalolithiasis by rotational stimulation is much inferior to the gravitational acceleration. (Imai T, et al. : Acta Otolaryngol 119: 24-28, 1999)

**BP3.2**

**Utricular dysfunction in patients with benign paroxysmal positional vertigo**

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Benign paroxysmal positional vertigo (BPPV) is provoked by displaced, mobile particles which have entered a semicircular canal. These particles most likely consist of utricular otoconia which have separated from the macula secondary to ageing, trauma, infection or ischemia. The objective of this study was to test the hypothesis that otolith function is impaired in patients with BPPV.

Methods and patients. Unilateral stimulation of the utricular maculae was performed on a rotator with the chair mounted on a translation plate which allowed eccentric lateral displacement of the patient during earth-vertical rotation. Thus, one labyrinth could be aligned with the axis of rotation while the other labyrinth was exposed to radial acceleration, resulting in unilateral stimulation of the eccentric otolith organ. Constant velocity rotation allowed decaying of semicircular canal response before testing was started. Eye movements were recorded with 3D video-oculography for measurement of the torsional otolith-ocular reflex. In addition, the static subjective visual vertical was measured. Twelve patients with unilateral idiopathic BPPV without a history of concomitant vestibular or neurologic disease were examined in the study. On average, patients were tested eleven days after successful treatment with the Epley or Semont maneuver and again one month later. The control group included 24 normal subjects.

Results. The peak-to-peak amplitude of torsional eye movements in response to cycles of left and right eccentric rotation was smaller in patients than in the control group ($p<0.05$). Ocular responses were less symmetric in patients compared to controls ($p<0.05$). However, there was no correlation between hypometric responses and the side of the ear affected by BPPV. Measurement of the static visual vertical was normal in all patients.

Discussion. Our study suggests that otolith function is impaired in patients with BPPV. This finding may account for the transient mild imbalance and dizziness which some patients with BPPV experience even after resolution of positional vertigo. Measurement of the otolith-ocular reflex showed a bilateral deficit with individual asymmetries that did not relate to the side affected by BPPV. Hence, an underlying bilateral degeneration of otolith function can be suspected in most patients with idiopathic BPPV.

**BP3.3**

**Vivid headshake can convert cupulolithiasis into canalolithiasis to be subsequently treated**

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While effective and prompt treatment for canalolithiasis has been achieved with various particle repositioning maneuvers or training programs, cupulolithiasis has remained a problem. The problem of a cupulolithiasis is that the canaliths adhere to the cupula, causing continuous symptoms and are generally not moveable by particle repositioning maneuvers. Patients have had to wait until a cupulolithiasis turned into a canalolithiasis spontaneously or by use of a training program because to treat a cupulolithiasis it has to be converted to a canalolithiasis.

The basics of all BPPV treatments rest upon the fact that the canaliths has a mass. If a mass adheres to the cupula robust movements may cause it to lose its adhesion and hence, turn into a canalith. We have tried this on selected patients that presented with symptoms in agreement with of both lateral, anterior and posterior canal cupulolithiasis. In some, but not all cases a vivid headshake of 20 to 30 sec may turn the cupulolithiasis into a canalolithiasis which is subsequently treated.

In video demonstration we show a patient with 4 months of disturbing positional vertigo and unsteadiness and positioning nystagmus in agreement with a lateral canal cupulolithiasis. A vivid headshake then converts nystagmus responses to those of a canalolithiasis and subsequent treatment relieves the patients. A second patient with 3-4 month of similar symptoms but where nystagmus responses may agree with an anterior canal cupulolithiasis is similarly treated and relieved of symptoms.

It is feasible to assume that the inertia of the mass of the canaliths may cause them to be separated from cupula if exposed to acceleration and decelerations of enough power.

If so, we may alleviate at least some patients with cupulolithiasis as effectively as we treat canalolithiasis.

**BP3.4**

**Experimental Study on Speed Dependent Positional Nystagmus of BPPV**

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A clinical characteristic of BPPV is that the more quickly the head position changes the more intense the vertigo. This suggests that the velocity of the head change is critical for determining the severity and the occurrence of vertigo.

Canalolithiasis and cupulolithiasis models were prepared using the bull frog posterior semicircular canal. The ampullary nerve discharges were compared between quick and slow positional changes to examine determining factors for BPPV symptom.

In canalolithiasis model, the accelerations of the otoconial movement was greater in the quick change. This resulted in the greater discharge with longer duration. In the slow positional change,the discharges were smaller and shorter. In cupulolithiasis model, the discharges were sustained and the magnitude was not different between the quick and slow changes. Canalolithiasis model influences the discharge magnitude of the PSC according to a speed of the positional change.

This suggests that canalolithiasis would be a more reasonable mechanism of BPPV which is characterized by various degrees of vertigo upon kinetic positional change.

**BP3.5**

**Evaluation of the Medical Care of Patients With Benign Paroxysmal Positional Vertigo**

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Background: Benign paroxysmal positional vertigo (BPPV) is the most common vestibular disorder which can be easily diagnosed. The evolution of highly effective positioning manoeuvres has made BPPV the most successfully treatable cause of vertigo.

Objective: To evaluate the medical care of patients with BPPV in Berlin/Germany.

Methods: Patients with BPPV of the posterior semicircular canal were evaluated retrospectively with regard to past medical history and disease-related diagnostic/therapeutic procedures. Forty-two patients were recruited from a specialised dizziness-clinic and a further 29 patients from a neurological practice. In all patients diagnostic positioning (Hallpike-test) evoked after a latency of a few seconds predominantely torsional positional nystagmus with a duration of less than 40 seconds. All patients were cured with either the Epley or the Semont manoeuvre. Patients with a second vestibular disease were excluded from the study.

Results: The mean duration of the disease was 3. 2 years with an average of 2. 4 episodes lasting typically several weeks to months. More than half of the patients felt severely disabled by BPPV and 25 % were temporarily unfit for work. On average, three different medical specialities were consulted. Audiometry (49%), caloric testing (46%), cerebral imaging (42%) and carotid Doppler ultrasonography (34%) was performed more often than diagnostic positioning (28%). Most patients received ineffective or no therapy and only 4% were treated with a specific therapeutic positioning manoeuvre.

Conclusions: BPPV is a long-lasting and frequently recurrent disease which leads to significant morbidity and medical costs. The recent progress in the diagnosis and therapy of BPPV has not yet been widely established in medical practice in Germany.

**BP3.6**

**Analysis of factors that affect the result of vestibular rehabilitation in the treatment of BPPV**

**G. C. Han**, H. G. Jeon, J. M. Huh
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Canalolith repositioning procedure(CRP)is the effective treatment for benign paroxysmal positional vertigo (BPPV). However, there are significant numbers of patients who require multiple treatment visits for relief of symptoms. The purpose of this study is to identify factors that may be associated with these difficult to treat cases.

Materials and Methods. A retrospective review was made of 179 patients who were diagnosed as BPPV. 20 patients who required more than three treatment visits for CRP were included in this study. Statistical analysis included age and sex of patients, the kind of involved semicircular canal (SCC), direction of nystagmus, latency of nystagmus on electronystagmography (ENG) and duration of symptoms before CRP.

Results. There was no significant statistical association between the number of treatment visit and patient's age, sex. Although significant statistical association was not found, the therapeutic efficacy of lateral SCC BPPV was lower than that of posterior SCC BPPV. In the cases of which the direction of nystagmus was ageotrophic, the efficacy of CRT was decreased and statistical significant association was found. Also when short latency of nystagmus on ENG and long duration of symptoms was appeard, more trial of CRP was needed and statistical significant association was found. Also when short latency of nystagmus on ENG and long duration of symptoms was appeared, more trial of CRP was needed and statistical significant association was found.

Conclusion. In the treatment of BPPV by CRP, we can consider latency of nystagmus on ENG, duration of symptoms, direction of nystagmus and type of involved semicircular canal as prognostic factors.

**BP3.7**

**Electronystagmographic analysis of horizontal canal type benign paroxysmal positional vertigo**

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The incidence of Horizontal canal BPPV(Hc-BPPV) in all BPPV was reported 6-22%. Recently, multicanal BPPV was reported increasingly also. But we don't know the exact relations between the eletronystagmographic findings and the physical findings of Hc-BPPV, yet. Therefore, we compare with geotrophic and ageotrophic nystagmus in Hc-BPPV.

Materials and Method. For 43 possible Hc-BPPV

patients of 198 dizzy patients (age 53 years ± 15. 5, Male:Female = 12:31), 20 patients with definitive Hc-BPPV were selected and electronystagmographic analysis was done. Diagnosis of Hc-BPPV was included with direction changing positional nystagmus without other central sign, head and body position that provokes the vertigo, response to repositioning maneuver and vertigenous symptoms nature. We compared with geotrophic nystagmus and ageotrophic nystagmus which was induced at each side of head position in supine by amplitude, frequency, correlation between amplitude and frequency, vertical nystagmus, slow harmonic acceleration(SHA) test, and latency and duration of primary nystagmus.

Results. The incidence of geotrophic nystagmus and ageotrophic nystagmus was 11:9. The difference of amplitude in both side head position was more considerable in agetrophic nystagmus than in geotrophic nystagmus(p-value=0. 000 : 0. 054). The difference of frequency in both side head position was more considerable in agetrophic nystagmus than in geotrophic nystagmus(p-value=0. 004 : 0. 183). The correlation of amplitude and frequency of in both head position were strong in both ageotrophic nystagmus and geotrophic nystagmus. Incidence of the vestibular weakness was counted more in geotrophic nystagmus than ageotrophic nystagmus from analysis of SHA test. In 11 cases of geotrophic nystagmus, vertical nystagmus was seen in all cases (upbeating/downbeating=9/2) and especially at the lesion side. In 9 cases of ageotrophic nystagmus, vertical nystagmus was seen in 7 cases (upbeating/downbeating=5/4) and at the healthy side. There was no significant difference between latency and duration of primary nystagmus in geotrophic nystagmus and ageotrophic nystagmus.

Conclusion. Ageotrophic nystagmus was induced by some more stronger stimulation than geotrophic nystagmus, and there was strong correlation between amplitude and frequency of induced positional nystagmus, therefore careful physical examination can make a exact diagnosis. Vertical nystagmus were showed at lesion side dominantly and these were almost upbeating type in geotrophic nystagmus especially. Therefore, geotrophic nystagmus might be induced by posterior canal type BPPV incidentally, and some ageotrophic nystagmus could be induced by anterior canal type BPPV incidentally. But further study will be needed in this conclusion. Canal weakness was more frequent in geotrophic nystagmus. The pathogenesis of vestibular weakness in BPPV may be attributable to otolith degeneration, but true cause is still unknown. Latency and duration of induced positional nystagmus is not significant.

**BP3.8**

**A New Treatment Strategy of Ageotrophic Horizontal Canal Benign Paroxysmal Positional Vertigo**

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Ageotrophic nystagmus in horizontal canal BPPV has been explained as a result of cupulolithiasis theory, and has been reported to have the less therapeutic response to conservative rehabilitations than the other type of BPPV . Though methods to detach the debris with vibrator have been introduced, the effect has been questioned and it is not physiologic.

Materials and Method. We introduce a new head shaking-forced prolonged position method as a more convenient method, and report 2 typical cases of ageotrophic horizontal canal BPPV managed with it and analyzed results of 25 cases all told.

Results and conclusion. The average number of rehabilitation was less than two, and loss of direction changing positional nystagmus could be observed immediately after rehabilitation.

**BP3.9**

**Four cases of pseudo Benign Paroxysmal Positional Nystagmus**

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Positioning nystagmus with a severe vertigo has been reported in patient with partial lesions of the inner ear, especially otolith lesions. Typically, it shows a latent period and subsequent fatigability. It is generally accepted that positional vertigo and nystagmus might result from lesions in the central nervous system. Lesions in central nervous system are often found dorsolateral to the fourth ventricle or in the cerebellar vermis. Recently we experienced 4 cases showing a positional nystagmus of paroxysmal type, resulted from lesions on the central nervous system and labyrinthine concussion due to temporal bone fracture. We present these cases of pseudo BPPN with literature review.

**BP4.1**

**Head Stabilization Strategy during Walking and Standing in Subjects with Vestibular Deficiency**

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The aim of the present study was to clarify the role of the vestibular system for head stabilization in space during conditions of static and dynamic equilibrium.

Nine healthy subjects and 6 subjects with bilateral labyrinthine deficiency (BLD) were studied. Thirteen infrared reflective markers were attached to the head, trunk (C7), hip and knee. First, the subjects were instructed to stay quietly in an upright stance on a force-plate. Second, they were instructed to walk on a treadmill at a constant speed while watching a point on the wall 1 m in front of them. The analysis of linear (medial/lateral, M/L; anterior-posterior, A/P; and vertical) translations and angular (pitch, roll and yaw) rotations was performed at each body segment by means of a video image processing system. Head fixation point (HFP) was also determined on the M/L and vertical planes.

During standing, BLD subjects had significant increases in pitch amplitudes at the head and knee, though there was no difference between BLD and healthy subjects in linear translations of any body segment studied. During walking, the head pitch and roll amplitudes were increased in BLD subjects. The amplitude of linear M/L translation was significantly larger at the head and trunk, whereas the amplitude of yaw diminished remarkably at C7 and at the hip joints.

These data show that the angle motion of each joint functions positively to stabilize the head in BLD subjects

during both standing and walking. In addition, the results suggest that gaze stabilization is accomplished by an active mechanism between head M/L translation and head yaw in BLD subjects, whereas vertical gaze stability is maintained by multiple systems, including vision.

**BP4.2**

**Relationship between the Timed Up & Go and reported falls in persons with vestibular disorders**

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Identifying persons with vestibular disorders who are at risk for falling is a challenging task. The purpose of this retrospective study was to attempt to determine if the Timed Up & Go (TUG) test and walking with head turns correlated with reported falls in persons with vestibular dysfunction.

One hundred three patient charts were included from a tertiary vestibular physical therapy practice. The patients ranged in age from 14-90 (mean=59; s. d. 17; 39 men/64 women). Fifty-two persons had peripheral vestibular diagnoses, 45 had central diagnoses, and 6 had both a peripheral and central diagnosis. Inclusion criteria were: a vestibular diagnoses, falls reported in the patient chart, and completion of either the TUG or the Dynamic Gait Index (DGI). Thirty-one persons reported falling one or more times in the previous 6 months during their initial assessment.

All patients were asked to stand from a standard chair, walk 3 meters, turn, and return to the chair. Time to complete the task was recorded. Patients also were asked to walk with head pitch and yaw movements and their score was recorded on an ordinal basis as part of the DGI. Scores of 3 were normal, 2 mildly abnormal, 1 moderately abnormal, and 0 meant that the patient could not complete the task safely. The relationship between independent variables and self-reported fall status was assessed with Pearson chi-square with odds ratios and 95% confidence intervals. Mantel-Haenszel chi squared statistic and adjusted odds ratios were used to assess the relationship in the presence of confounding variables such as age and vestibular diagnosis.

Persons who took longer than 13. 5 seconds to perform the TUG test were 3. 7 times more likely to have reported a fall in the previous 6 months (95% C. I. , 1. 4-9. 7, p=. 006. This relationship was present after adjustment for age (younger or older than 60 years, p=0. 02) and diagnosis (peripheral, central, or both, p=0. 02). Those who reported a fall were 2. 1 times more likely to score 0-1 on walking and moving the head in the yaw plane than a score of 2-3. Although not significant at p = 0. 05, the p value was p = 0. 09, 95% CI (. 88 to 5. 06). A faller was 2. 9 times more likely than a non-faller to score 0-1 on walking with head movements in the pitch plane (p = 0. 02, 95% CI (1. 2-7. 2)). This effect was also present after adjustment for age at 60 years (p=0. 05) and diagnosis (p=0. 05). Walking with yaw head movements did not discriminate between those who reported falling and those who did not, however pitch movements did relate to reported falls.

The TUG test appears to have considerable value for use in persons with vestibular dysfunction. Slower scores on the TUG (>13. 5 seconds) and walking and moving the head in the pitch plane are related to reports of falls in persons with vestibular dysfunction.

**BP4.3**

**Driving disability in patients with vestibular disorders**

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Driving is one of the most important daily life tasks performed by people in industrialized societies around the world. In most communities in North America the ability to drive a motor vehicle is essential for mobility within the community, to go to work, run errands, and participate in community activities. The ability to drive can be affected by sensorimotor impairments, including vestibular disorders. Although the literature includes several papers about physicians' beliefs about the driving skills of patients with vestibular disorders, no studies have examined pateints' experiences driving.

We surveyed patients with several vestibular impairments, including benign paroxysmal positional vertigo (BPPV), chronic peripheral vestibulopathy, Meniere's disease and post-vestibular nerve esction or acoustic neuroma, and compared them to a sample of normals. All subjects were interviewed using a well-normed instrument previously developed to evaluate elderly patients with vision impairment. Normal people report no significant deficits in driving skill. BPPV patients report few problems, as well. The other groups vary considerably but report more problems. The findings from the different diagnostic groups, compared to normals will be presented, including problematic driving situations and subjects' self-reported driving habits.

These results differ somewhat from physicians' beliefs about patients' driving skill. (Supported by NIH grants DC03602 and P50 AG11684-10. )

**BP4.4**

**New otolith functional test using eccentric center rotation**

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We have already presented the test of otolith function using eccentric center rotation. During eccentric rotation, subjects are given not only rotational stimulation but also linear stimulation. We have already shown that when the subject was facing outward, sinusoidal eccentric rotation at 0. 64Hz produced a significantly higher vestibulo-ocular reflex (VOR) gain than did on-axis rotation (Takeda et al, 1991). This finding suggests that the gain enhancement due to eccentric rotation is a result of tangential linear

acceleration.

In this study, we tried to estimate the function of otolith using eccentric center rotation when subjects faced to the ground. We analyzed 3D eye movements using our VOG system (Imai et al, 1999) when subjects were rotated on eccentric center chair facing to the ground. The subjects sat on the eccentric rotational chair setting their left ear out, right ear out, and head out against the center of rotation. In these situations, the rotational axis of eye is perpendicular to the ground about the rotational stimulation, and the axis is parallel to the ground about the linear stimulation. So eye movements can be separated into two components. One is against the rotational stimulation, and the other is against the linear stimulation. In light, during 0. 1Hz eccentric center rotation, eye rotation axis had the parallel and vertical component to the ground. This means eye movement responded to both stimulations, linear and rotational stimulation. But in dark, it had the vertical component to the ground, and didn't have the parallel component. This means eye movement respond to only rotational stimulation, not to linear stimulation. The results show that the eye movement during 0. 1Hz eccentric center rotation is induced by optokinetic eye movement, not by linear-VOR. In dark, during 0. 1Hz eccentric rotation, eye movement is induced only angular-VOR. But when the stimulation frequency is above 0. 5Hz, both in light and dark, eye rotation axis had both components, in a word, parallel and perpendicular component to the ground.

The results show that when the stimulation frequency is above 0.5Hz, the linear-VOR is activated. Eye movements had both components, against to linear stimulation and to rotational stimulation, and we could separate these two components. So we conclude that it is possible to assess the function of otolith using the analysis of eye movement that is induced during subjects are rotated above 0. 5Hz on eccentric center rotational chair facing to the ground.

**BP5.1**

**Identification of Asymmetric Vestibular Function Using a Pulse-Step-Sine Rotational Stimulus**

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Conventional clinical rotation testing typically uses sinusoidal or velocity step stimuli that evoke vestibulo-ocular reflex (VOR) responses to assess the function of the vestibular system. These stimuli are sometimes unable to detect an abnormality or, if an abnormality is detected, to identify the side of lesion. Therefore, we were motivated to develop a new type of quantitative rotation test that is better able to identify the side of lesion and assess the severity of a vestibular asymmetry.

A new Pulse-Step-Sine (PSS) rotational stimulus was designed to isolate and test vestibular semicircular canal function in each ear. The stimulus consists of 3 parts that perform 2 separate functions. The purpose of 2 of the parts, collectively referred to as the "bias" component, is to drive the neural activity of most afferents innervating one canal of a semicircular canal pair to zero during a portion of the stimulus cycle. This bias component consists of a pulse-step combination of rotational acceleration. The acceleration pulse (amplitude 400 deg/s2, duration 0.25 to 1s) produces a rapid increase or decrease in discharge rate of canal afferents from their resting rate. This pulse is followed by an acceleration step (10 to 38 deg/s2, duration 4 to 5 s). The acceleration step maintains a constant afferent discharge rate, at the increased or decreased rate produced by the preceding acceleration pulse, throughout the duration of the acceleration step. The third part of the stimulus, referred to as the "probe" component, consists of 3. 5 or 4. 5 cycles of a high frequency, low amplitude sinusoid stimulus (~1 Hz, 20 deg/s) superimposed on the acceleration step portion of the stimulus. The purpose of the probe component is to test the ability of the canals to encode the probe component motion during the period of the acceleration step, when most of the afferent activity in one of the canals is silenced. One complete cycle of the PSS stimulus lasts about 10 s and consists of both positive and negative acceleration components. Seven stimulus cycles are typically given during each test trial.

To understand how the PSS stimulus facilitates identification of asymmetric vestibular function, consider the following example. A subject with absent right-side vestibular function is rotated about a vertical axis with horizontal canals oriented perpendicular to the axis of rotation. If the bias component accelerations are large enough, rotation toward the right will silence neural activity from the left horizontal canal and maintain this silence throughout the duration of the step acceleration. Since right side function is absent, the vestibular system will not encode the probe component motion, and there will be no VOR eye movements related to the probe component of the stimulus. However, during rotations to the left, the afferent responses from the functional left canal are able to encode the probe component motion and generate VOR eye movements at the probe frequency. Data from normals and unilateral vestibular loss subjects are presented that demonstrate the effectiveness of this method.

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**BP5.2**

**Evaluation of outliers in a vertigo data set**

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Outliers are observations that are inconsistent with the rest of the data. A computerized method was applied to identify outliers within the six diagnostic groups of a vertigo data set (N=564). An expert physician evaluated whether these cases were truly unusual. Five batches of data (N=89), each containing roughly 50% of possible outliers, were presented to the expert who labeled each case as an outlier or a normal case by utilizing the patient's records and data collection questionnaire. The agreement with the method and the expert was 65%, and, also, the kappa coefficient 0. 30 (p=0. 006) indicated moderate agreement. Exclusion of Meniere's disease, which is a highly heterogeneous diagnostic group, increased the agreement. However, the agreement of 71% and the kappa coefficient 0. 43 (p=0. 003) indicated only moderate agreement.

The results give some evidence that our method identified unusual patient cases, but further tests are needed. Future research includes experiments where the expert evaluates cases using only the data given to the

computer. In addition, we should evaluate the consistency of expert's reasoning by presenting to him same cases several times or by presenting cases to another expert.

**BP5.3**

**Video image analysis system using a 4 times high-speed infra-red CCD camera**

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To analyze eye movements in three dimensions, we have developed a video image analysis system (VIAS). In this VIAS, the standard CCD camera with sampling frequency of 30Hz has been used. In this study, a high-speed camera, which has 4 times higher speed (120Hz sampling rate), is utilized to improve the accuracy of the analysis, especially for calculating torsional eye movements.

The output signals from a 4x high-speed CCD camera are directly fed into the memory of the computer. In order to capture 120 frames/sec accurately, an improved software has been developed. This software allowed us to catch all frames of images without any deficit and also without any reductions in the pixels of the images.

The 4x high-speed CCD camera is mounted on the specially designed light-weight goggles. The weight of the camera is 70g. The total weight of goggles with one high-speed camera is 250g. This weight permits us to fix the goggles to the head of the subject, and can be used during the dynamic head movements.

Conclusion. The VIAS with a 4x high-speed CCD camera is quite useful for studying human eye movements.

**BP5.4**

**The Video-impulse test allows assessment of vertical canal function in a clinical set -up**

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The vestibular head impulse test is useful to detect lesions of semicircular canal or vestibular nerve function. It may be performed with magnetic coil recordings system and by calculation of 3-D eye movements vertical canal function can be estimated. In clinical praxis head impulse test is performed under inspection of the naked eye and often restricted to evaluation of the horizontal VOR. The test however, is less sensitive to detect partial lesions and according to Shepard a caloric side difference of about 57% is needed to ensure a pathological test outcome.

Methods: We introduce the use of head impulses on patients using video nystagmoscopy goggles with a mask (Synopsis®) that allow one eye to be uncovered and to fixate in lateral or medial gaze. The subjects would fixate a mark on the wall at 1m distance to allow patients with presbyopsia clear vision. The other eye is covered with the CCD camera, which generates a close up image of the eye on the video monitor enhancing the possibility to detect a distorted VOR. By having the patients focus laterally to align gaze into the LARP (left anterior right posterior - canal) or the RALP (right anterior left posterior - canal) planes of the vertical semicircular canals, the otherwise 3-D VOR response evoked by vertical canal stimulation is transformed into a vertical 2-D movement. Head impulses are performed in the plane of the horizontal semicircular canal plane when focusing straight ahead and in the LARP and RALP plane when the eyes were focusing in the respective planes turning the evoked VOR into a vertical 2-D eye movement. Hence, the procedure allows estimation of all 6 semicircular canals in a clinical setting

Results: 40 patients with a vestibular schwannoma was investigated pre-op and had varying degrees of reduced caloric function. The video impulse test was always pathological when caloric function was reduced to 48% and usually detectable at 40%. In most patients it was possible to demonstrate engagements of the vertical canals. Furthermore, in single patients without reduced caloric function pathological head impulse tests were observed in the plan of the ipsilateral posterior canal. (which will be demonstrated on a Video)

Conclusion: By observing eye movements with video nystagmography it was possible to enhance sensitivity and evaluate all 6 semicircular canals in a clinical setting. We recommend the use of the video impulse test when evaluating patients with vestibular lesions.

**BP5.5**

**Video-oculography (VOG) in normal subjects**

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Our aim was to study spontaneous and positional nystagmus with infrared video-oculography recordings in normal subjects.

Twenty subjects without neurological and neuro-otological diseases were measured. There were 8 men and 12 women. Their age varied from 12. 6 years to 56. 4 years, mean 38. 3 years. Of the 20 subjects 1 was excluded because she fulfilled the criteria for migraine. Out of the remaining 19 subjects 79% had some kind of nystagmus during the testing, only 4 had no nystagmus.

The subjects were examined with 2 dimensional infrared computerized video-oculoscopy and the horizontal and vertical components of the nystagmus were studied. The subjects were measured in different head positions which were first in sitting position: the gaze in primary position, gaze 30 degrees to the left - forward, gaze 30 degrees to the right - forward, after head-shake, and in supine posiotion: first in supine position, Dix-Hallpike position backwards head to the left, Dix-Hallpike position backwards head to the right, and last with head turnings between 15 seconds to and fro. Each measurement lasted 30 seconds, but only in the last 90 seconds. Results were video-recorded. Nystagmus was noticeable only if at least 5 nystagmus beats could be identified. The nystagmus slow phase velocity (SPV) was calculated.

Spontaneous nystagmus was seen in altogether 4 subjects, 2 subjects had horizontal nystagmus (mean SPV 1. 5 degrees/s) and 3 vertical (mean SPV 1. 8 degrees/s). Gaze-evoked nystagmus was noticed in 4 subjects, in 3 subjects nystagmus was horizontal (mean SPV 1. 5 degrees/s) and in 1 vertical (SPV 1. 0 degrees/s). The horizontal gaze nystagmus was probable physiological end-point nystagmus. Rebound nystagmus, which was vertical, was seen only in 1 subject (SPV 1. 0 degrees/s). After head shake nystagmus was seen in 7 subjects, in 6 subjects nystagmus was horizontal (mean SPV 3. 5 degrees/s) and in

5 vertical (mean SPV 2. 8 degrees/s). At supine position nystagmus was seen in 4 subjects, 3 subjects had horizontal nystagmus (mean SPV 1. 3 degrees/s) and also 3 vertical (mean SPV 1. 0 degrees/s). Dix-Hallpike positions provoked nystagmus in altogether 6 subjects. One subject had horizontal nystagmus (SPV 2. 0 degrees/s) and 3 vertical (mean SPV 1. 7 degrees/s) at left Dix-Hallpike position. At right Dix-Hallpike position 2 subjects had horizontal nystagmus (mean SPV 2. 0 degrees/s) and 4 vertical (mean SPV 2. 5 degrees/s). Horizontal head turning provoked nystagmus in 6 subjects, in 4 subjects nystagmus was horizontal (mean SPV 1. 8 degrees/s) and in 5 vertical (mean SPV 2. 1 degrees/s).

In our study nystagmus was common among normal subjects in the dark, which has been seen in other studies too. Although nystagmus was very frequent, the SPV was of low velocity. No torsional component of the nystagmus could be seen in any subject. Nystagmus was most frequent after head shake. Although only horizontal and vertical components of nystagmus were studies, nystagmus was actually oblique in many subjects.

**BP5.6**

**Vestibular evoked potentials during active horizontal head rotations in patients with vertigo**

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The electroencephalographic (EEG) activity, angular acceleration of the head, horizontal and vertical eye movements were measured in 24 healthy human subjects and 43 patients with vertigo to stimulate the vestibular system. The evoked response (VestEP) in normal subjects was composed of six peaks, which were named by polarization and time difference from the trigger point (TP) P-100, N-30, P0, N50, P155, and N320. The EEG pattern was independant of the direction, of the type of target and of whether the eyes were open or closed. In contrast, the peaks, especially P155, were dependent on the chosen TP and the acceleration of the head rotations. In patients with peripheral vestibular disorders, P155 latencies correlated with an acceleration fo 20ms. Pontine vascular lesions revealed a homolateral P155 latency with a delay of 160ms while contralateral P155 latency remains normal. Space occupying cerebral tumors showed homolateral to the lesion an accelerated P155 latency of 30 ms and contralateral a 130ms prolonged p155 latency.

Our study has shown that it was possible to acquire characteristic EEG pattern during active head-rotations in the yaw plane. We could demonstrate, that VestEPs are able to discriminate between localized infra- and supratentorial cerebral lesion. Especially the peak P155 showed a reliance on acceleration. Additionally, vestibular dysfunction in diffuse cerebral diseases like SAE could not be correlated with a distinct VestEP pattern. We conclude that active horizontal head rotations are able to stimulate the vestibular system and may be used in the electrophysiological diagnosis of vertigo.

**BP5.7**

**Clinical balance assessment in 151 healthy subjects: age and gender effects**

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Patients with vertigo and balance problems can nowadays be investigated with extensive test batteries, including electronystagmography, otolith testing, vestibular evoked myogenic potentials, computerized posturography, etc. . . However, despite these sophisticated tests, there is still need for simple clinical tests that assess the functional capabilities of patients with balance problems, such as standing, turning and walking. Therefore, clinical tests such as the Timed Up and Go have gained interest for the evaluation of balance problems. This study is part of a larger study that investigates compensation after unilateral vestibular deafferentiation, using an elaborate test battery that includes several clinical and laboratory tests. We here report normative data for the clinical tests.

Methods. 151 healthy volunteers (mean age (SD): 42 (15) year, [21 013 77]) were evaluated with Romberg + Jendrassik manoeuvre (RJ), standing on foam (SOF) (eyes open (EO) / eyes closed (EC)), tandem Romberg (TD) (EO/EC), one leg standing (OLS) (EO/EC), past pointing test, Timed up and Go (TUG), forward functional reach (FFR), tandem stance (TS) (EO/EC), 10 meter walking, tandem gait (TG) (20 steps) and the dynamic gait index (DGI). Age- and gender effects are investigated using 2way ANOVA.

Results.

Quasistatic tests. All tests with eyes open could be performed by every participant. Two-way ANOVA revealed that for the task TS-EC an interaction effect between decade and gender was significant ($p=0.031$), next to the decade effect ($p=0.023$). Inspection of the data revealed that both men and women can perform this task easily up to their fifties, but later on the women showed a steeper decline in performance than men. OLS-EC showed to be more difficult since performance deteriorated for everyone in their forties.

Functional tests. We observed for the TUG and the 10m walking time a U-shaped behavior as a function of age. I. e. people in their twenties and thirties are more sluggish when told to stand up and walk for some distance, or to walk 10 meter, than people in their forties. At the age of 50 and higher, time to perform this task increases again, to even higher levels than for the younger ones. This U-shaped behavior was significant (quadratic model: $p<0.001$ for both TUG and 10m time). Additionally, a significant correlation exists between TUG and 10m walking (Spearman $rho=0.67$, $p<0.001$).

Conclusion. We conclude that when a global gait and balance assessment is performed in the vestibular and rehabilitation clinic, an age effect is apparent. Several tests, especially with eyes open condition, can be performed without problems by all subjects. Other tasks appear to be more difficult with increasing age. Moreover, the age effect is different for most of the tasks, with an awkward effect of vitality in the forties for the Timed up and Go and for the 10m walking. These conclusions should be taken into account when assessing patients with balance problems, using these kind of clinical evaluation methods.

**BP5.8**

**Vestibular neuritis visualized by 3. 0 Tesla MRI with triple-dose gadolinium - consecutive cases**

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Vestibular neuritis is a sudden idiopathic unilateral loss of vestibular function, usually affecting the function of the organs innervated by the superior vestibular nerve. It has been suggested that reactivation of herpes simplex type 1 virus or varicellae zoster virus could cause vestibular neuritis in a way that resembles Bells palsy and sudden unilateral hearing loss. Enhancement of the facial nerve on gadolinium-enhanced MRI is a common finding in Bells palsy and herpes zoster oticus. However, enhancement of the vestibular nerve has never been reported in vestibular neuritis. Here we report the finding of isolated vestibular nerve enhancement in two consecutive patients with vestibular neuritis, examined with 3. 0 Tesla MRI.

Methods. Vestibular and auditory tests: nystagmography and caloric tests, subjective visual horizontal, vestibular evoked myogenic potentials, vestibular impulse test and audiometry. Neuroradiologic examination on a 3. 0 Tesla head imager (Siemens Magnetom Allegra), with T1 sagittal, T2-flair axial and T2 coronal of the brain; and covering the internal auditory canal CISS axial and T1 axial (2 mm, TR 800, TE 15, matrix 192 X 256, 3 Acq) after standard dose Gadolinium-DTPA (0. 1 mmol/kg body weight) and triple dose (0. 3 mmol/kg body weight).

Case reports. A 66-year-old man woke with continuos rotatory vertigo and nausea. Investigations 3 days after onset of symptoms showed loss of function of the left superior and lateral semicircular canals and utricle with preserved function of the posterior semicircular canal and saccule, compatible with an isolated lesion of the superior vestibular nerve.

A 54-year-old woman fell ill with rotatory vertigo,nausea and vomiting. Investigations 4 days after onset of symptoms showed loss of function of the right superior and lateral semicircular canals and utricle, compatible with a lesion of the right superior vestibular nerve

Seven and eleven days after symptom onset the respective patients were examined in a 3. 0 Tesla head imager. With standard doses of contrast agent no clear-cut pathologic findings were revealed. Triple-doses of Gadolinium-DTPA revealed enhancement of the left vestibular nerve in the man and of the right vestibular nerve in the woman. No abnormalities of the nerve were found on the CISS images and there were no enhancements of the membranous labyrinths.

Conclusion. To the best of our knowledge, this is the first time that isolated contrast enhancements of the vestibular nerve have been visualized on MRI in patients with vestibular neuritis. These findings support the hypothesis of a local inflammation of the vestibular nerve or ganglion in vestibular neuritis. Previous MRI-studies of vestibular neuritis used lower contrast doses and field strengths. By increasing the field strength and the contrast dose, the signal to noise ratio and sensitivity increase.

**BP5.9**

**Galvanic stimulation in patients with unilateral vestibular deafferentation: comparison of test results**

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Galvanic stimulation has been used for vestibular testing. Galvanic body tilts and galvanic evoked vestibulo-collic reflex tests are now in clinical use. These tests could be useful for differential diagnosis of labyrinthine lesions from retro-labyrinthine ones. However, there is no report concerning the agreement of the lesion site indicated by the galvanic evoked vestibulo-collic reflexes testing with the lesion site indicated by the galvanic body tilts testing. If two tests indicate the identical lesion site, the results of these tests would be more reliable. Herein, we compared test results of galvanic evoked vestibulo-collic reflexes with those of galvanic body tilts tests.

Materials and Methods. Eight patients with unilateral vestibular deafferentation (3 females and 5 males, 30 to 68 years of age) were enrolled into this study. Unilateral vestibular deafferentation was diagnosed by absent caloric nystagmus and absent vestibulo-collic reflexes evoked by click in one side. Their clinical diagnoses were vestibular neuritis in one patient, acoustic neuroma in 3, Ramsay Hunt syndrome in 1, post-labyrinthectomy in 1, sudden deafness with vertigo in 1 and juglar foramen neuroma in 1. We reviewed their test results of galvanic evoked vestibulo-collic reflexes (3mA, 1msec) and galvanic body tilts (1mA, 5sec)

Results. All patients had normal responses in both tests on the unaffected side. Galvanic body tilts were abnormal in 7 (absent in 6, decreased in one). Out of the 7 patients, galvanic evoked vestibulo-collic reflexes were abnormal in 6 (absent in 4, decreased in 1, and prolonged latency in 1). One patient had abnormal galvanic body tilts but normal galvanic evoked vestibulo-collic reflexes. One patient had normal galvanic evoked vestibulo-collic reflexes and normal galvanic body tilts. In other words, both tests indicated retro-labyrinthine lesions in 6 patients and labyrinthine lesions in 1 patient. Only in one patient different lesion sites were suggested by two tests.

Conclusion. In this small pilot study, we found agreement of the lesion site indicated by galvanic-evoked vestibulo-collic reflexes with that by galvanic body tilts. This result implys that both tests might be useful for the differential diagnosis of labyrinthine lesions from retro-labyrinthine lesions in patients with unilateral vestibular deafferentation and that we might be more confident about the lesion site by agreement of lesion sites indicated by the 2 tests.

**BP5.10**

**The 3-D eye-movement response in patients to maintained surface galvanic vestibular stimulation**

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In previous studies with normal subjects, we have shown that the eye-movement response to GVS is idiosyncratic, but quite repeatable; that normal subjects show symmetrical responses to GVS delivered to the left or right mastoid and to anodal or cathodal current polarities; that the magnitude of an individual's eye-movement response to GVS is a linear function of the magnitude of

the current passed; that individuals have their own sensitivity or gain function; that the response in darkness to bilateral GVS stimulation seems to be a simple sum of the responses to unilateral stimulation of each side; that there exists adaptation and an overshoot in response to the offset of GVS and that there also seems to be slow decay of these eye-movement responses, with time constants of some hundreds of seconds .

These principles have formed the basis of a heuristic model of eye-movement responses that uses a simple linear addition of the weighted contributions from each vestibular sensory region. The model outputs accurate representations of the responses of normals, and generates novel predictions about the idealised responses that are expected due to various kinds of known vestibular dysfunction. In each case, the response predicted by the model is derived by modifying the contribution of the sensory regions affected by the dysfunction (e. g. minimising the contribution of all endorgans on the left in the case of a patient with surgical unilateral loss on the left). The idealised response could then be tuned to the subject's observed response by making symmetrical modifications to the activation of sensory regions, within a range consistent with the variability seen in a normal population.

Patients diagnosed with some of these kinds of vestibular dysfunction have been tested, and their responses to GVS have been consistent with the model's predictions. The results of the present study lend weight to the validity of the model and thereby support the argument that surface GVS tends to stimulate all endorgans to various degrees and in an idiosyncratic, yet predictable, fashion. It should be noted that a lack of response to GVS could result equally from normal variations in factors such as impedance paths between delivery at the surface and stimulation at the spike trigger zone, or abnormal disruptions anywhere along the path from the spike trigger zone through central processes and oculomotor output. The absence of eye-movement response to GVS does not, therefore, necessarily implicate endorgan dysfunction. In contrast, the presence of an eye-movement response to GVS indicates effective delivery of the stimulus as well as entailing the function of everything upstream from the site of activation. For example, patients may show a GVS response from endorgans even after undergoing surgical ablation if some afferent terminals remain. Patients with vestibular loss which has been inferred from other tests may, therefore, still show responses to GVS, and vice versa. In that all clinical tests are imperfect, accurate diagnosis is therefore likely to remain a question of evidence from a number of sources.

**BP5.11**

**The Clinical Significance of Head-shaking Nystagmus in the Patients with Acute Vestibular Loss**

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In unilateral peripheral vestibular loss patients, head-shaking induce a bias from remaining aymmetric vestibular sensor and cause the imbalance in velocity-storage mechanisms. Head-shaking Nystagmus(HSN) is the transient nystagmus induced by shaking the head in the horizontal plane for a few seconds and have slow phases directed toward the side of vestibular loss. We evaluated the usefulness of the HSN in acute unilateral peripheral vestibular loss patient with reference to spontaneous nystagmus(SN), bithermal caloric test, and slow harmonic acceleration(SHA) test.

Materials and Methods. 18 patients of acute unilateral peripheral vestibular loss(nine vestibular neuronitis, four acute unilateral ototoxicity, two sudden sensorineural hearing loss, one acute suppurative labyrinthitis, one vestibular neurectomy, one Ramsay-Hunt syndrome) who had SN and symptoms of acute prolonged vertigo were analyzed retrospectively. The examiner performed passive head rotation in 30 degree anteflexed position with eyes closed and oscillated about 60 degree to each side, 2 Hz for 20 cycles. The nystagmus was observed with Frenzel glasses immediately after head was stopped and more than three consecutive beats of nystagmus were considered a positive. SN were recorded with video-nystagmography. We defined a positive if CP>25%, DP>30% in bithermal caloric test. Low gain and asymmetry in SHA test were defined abnormal if abnormalities were recorded in more than two consecutive frequencies.

Results. The prevalance of HSN was 89% (16/18). During follow-up period, direction of nystagmus was changed 28%(13/18) in SN, but in HSN, direction was fixed in all subjects. SN and HSN directed toward the same side in 75%(12/16) but in four cases(25%), direction could not compared because the direction of SN was changed during follow up peroid. In 69%(11/16) of subjects, HSN persisted after the disappearance of SN. In comparison of HSN with bithermal caloric test, direction of CP was highly correlated with direction of HSN(92%) but not with SN(64%). HSN was more prevalent(92%) than DP(57%) in caloric test and asymmetry(78%) in SHA test.

Conclusions. HSN test, easily performed office maneuvers, is very useful method to identify the laterality of acute unilateral peripheral vestibular loss, especially in chronic stage.

**BP5.12**

**Vibration Induced Nystagmus**

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The finding of a Vibration Induced Nystagmus (VIN) after stimulating the mastoid, vertex and or dorsal neck has been considered as a sign of unilateral vestibular deficit in patients with vertigo. The purpose of this work is (1) to elaborate criteria to discriminate the findings of normal vs abnormal, and (2) to show our results after applying this stimulus in a group of patient with vertigo.

Subjects. (1) 25 normal subjects without previous dizziness and normal hearing with normal head thrust maneouver and normal caloric test and (2) 125 consecutive outpatients complaining about vertigo. Criteria for exclusion were considered in order to detect, and exclude from the study, patients with bilateral lesions. After a detailed history and a complete neuro-otological bedside examination that included the Head-Thrust, caloric test, rotatory test and, Sensory Organization Test of the Dynamic Posturography, were perfomed.

Method. A customary vibration stimulator oscillating at 100 Hz was applied to the mastoid (right and left), to the vertex and, to the dorsal neck stimulating the muscle bulk (right and left). The result was analyzed with the

videonystagmography system. Each stimulation was maintained for 30 seconds and was preceded by 30 seconds of recording without stimulation in order to define the existence of Mastoid Vibration Induced Nystagmus (MVIN), and Dorsal Neck VIN (DNVIN) in the right (R) and left (L) and, Vertex VIN (VVIN). The velocity of the slow component of the nystagmus evoked and the direction of the fast phase were used to describe the nystagmus. The results were analyzed in terms of VIN+ vs VIN- and the direction of the nystagmus as direction fixed, direction changing and Nystagmus in 1 mastoid.

Results. 83% of the normal subjects displayed some nystagmus after stimulation. When it was in 3 or more stimulations, whenever direction fixed or direction changing, slow phase velocity was lower than 2º/s and when found after only 1 stimulation it was lower than 4º/s. With these data in mind, criteria for abnormality were considered and in 36% of the patients VIN was regarded as pathologic. Specificity and sensitivity is analyzed with regard to different measurements.

Conclusions. VIN is a common finding in normal subjects; however, with proper criteria it can be regarded as a vestibular sign and found in 36% of the patients seen because of vertigo.

**BP5.13**

**Assesment of perilymphatic fistula. An animal model with MRI**

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This study was designed to study methods to diagnose and visualize perilymphatic fistula. An animal model was created in which the accuracy of endoscopic technique was compared with microscopic evaluation of round window (RW) fistula. Thereafter the accuracy of magnetic resonance imaging (MRI) in assessing perilymphatic fistula (PLF) was studied in the model.

Methods. In guinea pigs, a tear in RW was made with a glass micropipette or with laser beam and results were compared with 1. 8 mm otoendoscope and microscope. The PLF was studied in 4. 7 T experimental MRI (Bruker Biospec Avance 47/40) with gadolinium (Gd-DTPA-BMA) administration among 14 guinea pigs Three with i. v. administration, 3 with middle ear catheters and 8 with transtympanic injection. In 5 of the transtympanic injection animals external pressure loading was performed with Siegle speculum to facilitate the penetration of Gd-DTPA-BMA into perilymph. The middle ear was inspected with otoendoscopes with 5 deg and 30 deg of visual angle and compared with microscopic picture.

Results. In all animals the endoscopy was equally accurate as microscope in assessing PLF, if PLF was inspected through the endoscope. On the monitor screen some of the fistulas were not visible due to resolution of videocamera on the endoscopes . In MRI the PLF leak was visible in most animals. The Gd-DTPA-BMA appeared after variable latency in the perilymph when delivered with catheter or transtympanic injection. In animals without external pressure the intact side usually (2 out of 3) loaded the Gd-DTPA-BMA faster than the PLF side. In pressure facilitated animals the middle turn loaded poorer Gd-DTPA-BMA in PLF side that in intact side, but the vestibulum loaded faster Gd-DTPA-BMA in 4out of 5 PLF animals. In i. v. administrated animals the PLF side tended to load Gd-DTPA-BMA faster than intact side.

Conclusions. Tympanoscopy should be regarded as the first choice when a PLF is suspected. MRI is a new measure that is promising in assessing PLF but the Gd-DTPA-BMA administration method should be refined. The small molecular size of Gd-DTPA-BMA allows fast penetration through the RW. The loading of perilymp in the intact inner ear was faster than in the leakage side. In transtympanic injection probably a contrast agent with molecular size larger than Gd-DTPA-BMA could show the PLF. The i. v. application may be the method in human for visualizing the PLF.

**BP5.14**

**In vivo visualization of endolymphatic hydrops in guinea pig**

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The recent magnetic resonance imaging (MRI) technique has made it possible to examine the cochlear compartments by using gadolinium-DTPA-BMA (Gd-DTPA-BMA) contrast agent. As the Gd- DTPA-BMA does not enter into the endolymph but loads the perilymph the technique provides possibilities to visualize the different cochlear compartments. The purpose of the study was to evaluate whether it is possible to visualize experimental endolymphatic hydrops in the cochlea using MRI

Methods: The cochleae were studied in 4. 7 T experimental MRI (Bruker Biospec Avance 47/40) with Gd-DTPA-BMA administration among 16 guinea pigs. Five normal guinea pigs were used as controls. Early manifestation of endolymphatic hydrops was evaluated in endolymphatic sac-intact animals (n=6), and advanced manifestation in endolymphatic sac-damaged animals (n=5). Hearing was tested with electrocochleography. The surface area of three partitions of the cochlea was used to quantify endolymphatic hydrops. After the experiments the animals were sacrificed and the cochleae were studied histologically. For quantification of EH areawith density measurement and angle of Reissner's membrane was calculated.

Results. The fine structure of the three partitions of the cochlea was visualized with MRI in all animals as Gd-DTPA-BMA appeared mainly in scala tympani and vestibuli. As early as 5 days after endolymphatic sac surgery, endolymphatic hydrops started to appear as visualized by MRI and also verified with histology. Severe damage to the inner ear barrier with Gd- DTPA-BMA leakage into scala media was detected with MRI in one endolymphatic sac-damaged animal who had a 60 dB hearing loss. The values were pathological in all visually confirmed hydrops animals and in addition in one visually normal ear it was pathological. In all cases hydrops could be verified visually. The evaluation of the position of Reissner's membrane was not as accurate as area with the density evaluation method.

Conclusions. Endolymphatic hydrops can be visualized with high resolution MRI by using Gd- DTPA-BMA and it is possible to quantify the extent of endolymphatic hydrops. Damage to the inner ear barrier or

possible rupture of membranes can be shown with the assistance of Gd-DTPA-BMA. Area and density evaluation seem to be accurate methods in evaluation of hydrops.

**BP5.15**
**Episodic Vertigo and Ataxia and Mutations in CACNA1A**
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Episodic ataxia type II (EA2) is a dominantly inherited disorder characterized by early onset episodes of vertigo and ataxia lasting hours to days with interictal eye movement abnormalities. The attacks are commonly triggered by fatigue or emotional stree and can be dramatically responsive to acetazolamide, a carbonic anhydrase inhibitior. Since the identification in 1996 of point mutations in the calcium channel subunit encoding gene, CACNA1A, on chromosome 19P in patients with EA2 and familial hemiplegic migraine (FHM), several groups have reported additional mutations in this gene. In the past it was felt that mutations causing FHM were missense while mutations in CSCNA1A in a large group of patients with episodic vertigo and ataxia and in a group of patients with migraine and episodic vertigo but without ataxia or interictal nystagmus.

For mutation screening, we used SSCP (Single strand confirmation polymorphism) and denaturing HPLC followed by sequencing. We identified 14 new mutations (4 missense, 5 nonsense, 2 splice site, and 3 deletions) in 11 families and 3 sporadic cases with the EA2 clinical profile. We found no mutations in CACNA1A in patients with migraine and vertigo and ataxia and interictal nystagmus, a few patients with mutations in CACNA1A also exhibited myasthenic episodes and epileptic seizures. We also studied 5 families with atypical EA2 (3 with late onset episodic ataxia and intertical nystagmus and 2 with early onset episodic ataxia but not interictal nystagmus) and fuled out linkage in these families to the 19P locus. Thus, there is genetic heterogeneity with EB3.

Conclusion. 2 can be caused by several different types of mutations, and we did not find a simple genotype-phenotype correlation to explain the clinical variability. We also demonstrated clear genetic heterogeneity with EA2 and we did not find any mutations in CACNA1A in paitents with uncomplicated migraine. The mutations associated with EA2 were distributed throughout the highly conserved membrane spanning segments of the protein. Efforts are underway to study the functional (biophysical and cell biological) consequences of these mutations.

**BP5.16**
**Vestibular Evoked Myogenic Potentials in Response to Skull Taps**
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In recent years it has been demonstrated that midline forehead skull taps generate short latency vestibular evoked myogenic potentials (VEMP), similar to those evoked by click sounds. It has been proposed that skull tap induced VEMP are valuable in vestibular testing as a supplement to testing click induced VEMP because the response is not attenuated by middle ear conduction abnormalities.

In the present study, gentle skull taps were delivered manually on the forehead and above each ear. The responses were recorded using skin electrodes over both sternocleidomastoid muscles. The groups tested were 13 normal subjects, five patients at long-time follow-up after unilateral labyrinthectomy, and 20 patients during the first week after onset of vestibular neuritis.

Among the normals, forehead tap stimulation evoked a bilateral positive-negative VEMP (i. e. of the same polarity seen in response to click sounds). However, at laterally directed skull taps they showed "coordinated contraction-relaxation responses", i. e. skull taps on one side evoked a negative-positive (inverted) response on that side and a positive-negative (normal) response on the contralateral side.

Among the patients who had undergone labyrinthectomy, midline forehead skull taps evoked responses similar to those seen at laterally directed skull taps in normals, i. e. positive-negative VEMP on the healthy side but negative-positive VEMP on the operated side. The same type of coordinated contraction-relaxation responses were seen when laterally directed skull taps were delivered above the operated ear. However, such coordinated responses were not seen at skull taps above the healthy ear.

In the group of patients with vestibular neuritis 11/20 showed a pathologically reduced VEMP. In response to forehead skull taps there were reduced VEMP on the lesioned side. Moreover, in response to laterally directed skull taps there were weaker VEMP to skull taps above the healthy compared with skull taps above the lesioned ear.

These findings suggest that VEMP in response to skull taps are valuable in vestibular testing. The present findings also suggest that laterally directed skull taps mainly activate the contralateral labyrinth.

**BP5.17**
**Galvanic-Evoked Myogenic Responses of Healthy Volunteers**
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Vestibulo-collic reflexes (VEMP) by clicks have been used as a clinical test of the vestibular system. However we have not been able to determine the site of the lesion responsible for the lack of reflex, which is one of the abnormal responses. Recently it has been shown that galvanic stimulation also evokes myogenic responses on the sternocleidomastoid muscle (SCM). It is suggested that galvanic stimulation would stimulate the most distal portion of the vestibular nerve while the clicks would act at the receptor level. On the basis of this supposition, it has been suggested that galvanic-evoked myogenic responses might be useful in differentiating labyrinthine lesions from retro-labyrinthine ones in patients with an absence of VEMP by clicks. Prior to clinical studies, studies of normal subjects are required. Herein, we report galvanic-evoked myogenic responses on the SCM of healthy volunteers.

Materials and Methods. We studied the average responses in the unrectified electromyographic (EMG) activities of the SCM to galvanic stimulation. The cathodal electrode was on the mastoid, and the anodal electrode was on the forehead. Twenty-two healthy volunteers were

studied. We used 3mA (1ms) galvanic stimulation. EMG activities were amplified and band pass-filtered (20-2000Hz). The stimulation rate was 5Hz, and the analysis time was 50msec. The responses to 50 stimuli were averaged twice with and without contraction of the SCM by raising the head in the supine position. To remove artifacts, we subtracted the average obtained without contraction of the SCM from the average obtained with contraction of the SCM. In some subjects, thresholds of responses to galvanic stimuli and effects of the repetition rate were also observed.

Results. In all the healthy volunteers, mastoid-forehead galvanic stimuli produced a positive-negative biphasic response, which resemble VEMP by click stimuli, on the SCM ipsilateral to the cathodal electrode. The means +SDs of the latencies of the first positive peak (p13g) and the first negative peak (n23g) were 10.9 + 1.0 ms and 18.8 + 2.4 ms, respectively. The mean + SDs of the amplitude of p13g-n23g was 143+66 μV. Subjects' age did not have effects on the amplitudes of p13g-n23g. We also evaluated the percent galvanic-evoked myogenic potential asymmetry (percent GA) as 100 (Ar-Al)/(Ar+Al), where Ar is the p13g-n23g amplitude on the right, Al is amplitude on the right. The mean + SDs of the percent GA was 17. 8 + 10. 5. The thresholds ranged from 1. 0mA to 3mA. As the repetition rate, 5 Hz may be the best for recording.

**BP5.18**

**Myogenic potenials generated by short tone bursts in the soleus muscle**

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The aim of this study was to clarify whether we can record myogenic potentials in the soleus muscle by short tone bursts and whether those potentials are of vestibular origin. Normal volunteers and patients with vestibular disorders were enrolled into this study. In order to record potentials, surface electrodes were placed on the belly of the soleus muscle and around the Achilles tendon. During the recording subjects were instructed to stand on tiptoe and to turn the neck toward the stimulated ear. Five hundred Hz short tone bursts (plateau time=2 msec, rise/fall time=1 msec, 95 dBnHL) were presented through a headphone. Frequency of stimulation was 5 Hz. Signals were amplified and bandpass-filtered (20-2,000 Hz). One hundred responses were averaged. Analysis time was 100 msec.

Normal subjects showed biphasic myogenic potentials in the soleus muscle ipsilateral to the stimulated ear. The first negative peak with a latency of 57 msec, on average, was observed in the soleus muscle ipsilateral to the stimulated ear, followed by the positive peak ( latency of 70 msec, on average. Some patients with vestibular disorders showed absence of these responses.

These results indicated that 500 Hz short tone bursts could bring excitatory inputs to the soleus muscle ipsilateral to the stimulated ear and that these inputs might be of vestibular origin.

**BP5.19**

**The Natural History of Vestibular Schwannomas**

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Although microsurgery is usually performed on vestibular schwannomas, there are certain number of patients in whom no treatment is indicated because of age, unwillingness of surgery, complication etc. By our previous study on the tumor growth rate of 42 vestibular schwannomas, it was revealed that more than 60 % of the tumors showed very slow growth rate of lesss than 1 mm/year and in about 30 % of the tumors, growth was not recognized over 2 or more years. Our current policy on the management of vestibular schwannomas is that surgery is indicated for tumors larger than 15 mm in maximum diameter or tumors in which growth is confirmed after 6 months of follow up by MRI, and also for small tumors when the patient wants hearing preservation. The wait and see policy is applied to other patients unless he/she wants a tumor removed immediately.

We have operated on more than 200 cases and, at the same time, we have about 120 cases in wait and see policy over 2 or more years. Serial MRI scan is performed every 6 months for 2 years and every 1 year thereafter. The CISS MR imaging with sub-millimeter spatial resolution is mainly used in order to measure accurate size of the tumor. In more than 70% of the cases, tumor growth is not seen or barely seen. Some patients have hearing deterioration, which has no correlation with tumor growth rate. In two patients, tumor regression was seen.

In this paper, the natural history of vestibular schwannomas by exact measurement in relation to the change of hearing and vestibular function will be reported, and the strategy for management of these tumors including microsurgery and stereotactic radiotherapy will be discussed.

**BP5.20**

**Change in Dizziness Handicap following Vestibular Schwannoma Excision**

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Objective: To evaluate the change in dizziness handicap following translabyrinthine vestibular schwannoma excision
Study design: Prospective administration of the Dizziness Handicap Inventory (DHI) pre-operatively and at 3 and 12 months post-operatively; retrospective review of case notes.
Setting: A tertiary referral neuro-otology clinic.
Patients: A total of 100 consecutive patients who had vestibular schwannomas excised between June 1998 and Novemer 2001 and who had completed DHIs pre-operatively and at 3 and 12 months post-operatively.
Interventions: Translabyrithine excision of a unilateral sporadic vestibular schwannoma; pre- and post-operative generic vestibular rehabilitation exercises.
Main Outcome measures: DHI scores
Results: Dizziness handicap becomes significantly worse between pre-operative and 3 months post-operatively, but then does not continue to decline. Tumour size, gender, and magnitude of pre-operative canal paresis significantly affect the degree of change in handicap. Age, the presence of central vestibular system abnormalities and the nature of the patient019s principal presenting symptom have no effect upon this handicap change.
Conclusions: These findings help the clinician in counselling the patient pre-operatively about dizziness

handicap to be expected post-operatively. In particular the clinician is now able to take an informed and positive stance in the event of a severe canal paresis pre-operatively.

**BP5.21**
**Dynamic Bielschowsky Head-Tilt Test**
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A positive Bielschowsky head-tilt test (BHT) is the cardinal finding for diagnosing unilateral trochlear nerve palsy (uTNP): Tilting the head towards the paretic eye leads to an increase of vertical-torsional deviation between the two eyes. In clinical use, this test is performed in a static fashion, comparing the vertical deviation upon head tilt to both sides. To determine the instantaneous ocular rotation axes in patients with uTNP, we applied BHT in a dynamic fashion. 11 Patients with uTNP and 11 healthy subjects were asked to monocularly fix upon targets on a Hess screen, while they were rotated about the roll axis on a motorized turntable (&#177 35 &#186, 0. 3 Hz). 3D eye movements were recorded with dual search coils. Under viewing condition, the rotation axis of both the healthy and the paretic eye of patients with uTNP was close to the line of sight. The rotation axis of the covered fellow eye, however, followed gaze direction as well, but systematically deviated towards the nose relative to the line of sight (covered palsied eye: 16. 9 &#186 &#177 5. 8 SD, covered healthy eye: 17. 0 &#186 &#177 6. 9 SD, values for gaze straight ahead). Rotation axes remained stable during head roll.

The nasal deviation of the rotation axes can be explained by the lacking contribution of the superior oblique muscle to ocular counterrolling, if the palsied eye is covered, and an overaction of the contralateral inferior rectus muscle (yoke muscle), if the healthy eye is covered. This phenomenon represents a kinematical consequence of Hering's law. In conclusion, in patients with uTNP, the vertical-horizontal trajectories of the covered eye on the Hess screen during dynamic BHT are a direct consequence of the nasal deviation of the ocular rotation axes from the line of sight (see figure). - Supported by Swiss National Science Foundation (32-51938. 97 / 31-63465. 00) and Koetser Foundation for Brain Research (Zurich, Switzerland).

**BP5.22**
**Proposal for a Multi-Layer Ontology to Aid in Classification of Vestibular Disorders**
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Well-designed, internally consistent, and face-valid disease classification systems are necessary for both research and clinical purposes. Inconsistent use of nomenclature in defining vestibular disorders has plagued clinicians and hampered vestibular research, prompting efforts to create an International Classification of Vestibular Disorders. Although a multi-axial classification scheme similar to DSM-IV for psychiatric disorders was discussed at a recent international meeting as a possible solution, this structure was rejected as 'a way of describing symptoms… with no respect to etiology.' We propose a new multi-layer ontology that bridges the gap between clinical symptoms, underlying pathology, and etiology that could be used as a framework for an International Classification of Vestibular Disorders.

In order to build a new classification system for disease (a 'nosology'), we must first have a notion of how to represent information within that system. The implicit assumption in most such nosologies is that a 'disease' is a single entity – i.e. some specific 'cause' (etiology) leads to some sort of ill 'effect' (pathology or pathophysiology) that leads to 'manifestations' (clinical symptoms or signs), all in more-or-less sequential, linear fashion. Unfortunately, there are relatively few clinical vestibular disorders associated with a defined etiology that would fulfill Koch's postulates for causality and conform to such a straightforward, unitary concept of disease. Many vestibular disorders are defined solely on the basis of clinical symptoms (e.g. psychogenic vertigo). With other vestibular disorders, pathologies identified by temporal bone histology in a handful of autopsied cases have tacitly become incorporated into disease definitions without adequate evidence to support their specific association with a particular clinical syndrome (e.g. pathologic 'labyrinthitis' and the clinical syndrome of 'acute peripheral vestibulopathy'). Such anchoring of clinical disorders using mechanistic disease names may tend to thwart exploration of alternate pathophysiologic hypotheses – for example, might some so-called cases of 'labyrinthitis' actually have an ischemic pathogenesis? The unitary notion of 'disease' has been thrown into further turmoil by recent advances in the understanding of heritable mono- and poly- genetic disorders. The influence of disease-modifying genes and environmental factors complicate most, if not all, medical disorders, including those that affect the vestibular system (e.g. vestibular migraine).

In an effort to address the evolving scientific issues that disrupt the linear 'one etiology + one pathology + one clinical syndrome = one disease' concept, we have developed an explicit, multi-layer framework for representing 'diseases' and disease-related information as they relate to clinical practice. This effort is in keeping with the current state of the art in medical ontology, as represented by SNOMED® (http://www.snomed.org/) and GALEN (http://www.opengalen.org/). However, we have chosen an ontological structure that is likely to be conceptually straightforward to most clinicians, and maintains use of familiar disease 'labels.' We believe that such a framework, once validated, could aid both in bedside codification of clinical information and subsequent development of an International Classification of Vestibular Disorders.

**BP5.23**
**Building A New Model for Diagnosis of Dizzy Patients in the Emergency Department**
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Recognized, preventable medical errors are estimated to account for 44,000-98,000 deaths annually in the U.S. In the Emergency Department [ED], errors in diagnosis may

represent the majority of errors. Although in the outpatient setting fewer than one in ten cases of dizziness is attributed to a "serious cause" such as cerebrovascular accident (6%) or cardiac dysrhythmia (1.5%), in the ED up to 25% of patients over age 50 may have ischemic stroke as a cause of new, isolated vertigo. *It is in the ED setting, therefore, that there is an added premium on accurate diagnosis and a need for simple bedside methods to identify those at greatest risk*.

The dominant paradigm for the evaluation of the dizzy patient is based upon a 'pathophysiologic' approach that relies heavily on the assumption that the *quality* of symptoms reflects the underlying disease mechanism. In the tertiary-care setting, the quality of the dizzy symptoms represents a 'first-pass approximation' of the underlying disease process. This approximation is then refined through multiple iterations that rely on exhaustive bedside and laboratory testing. This 'pathophysiologic' approach is poorly suited to the ED environment, where evaluations are time-pressured and oriented towards ***triage*** rather than ***diagnosis*** – "Can this person be sent home safely, or do they need to be admitted?" In the ED, the quality-of-symptoms-oriented approach cannot be carried through to its meticulous extremes and may be abridged after the initial qualitative classification of dizziness as vertigo, presyncope, imbalance, or nonspecific dizziness. A faulty triage decision may then be made on the basis of this 'first-pass approximation.'

We have developed a prototype for an alternative approach to the ED dizzy patient. Our **'triage' approach** represents a shift of emphasis from the widely practiced 'pathophysiologic' one. Although we do not believe that the quality of dizzy symptoms offers *no* diagnostic information, the 'triage' approach we have outlined relies relatively little on the quality of symptoms and fairly heavily on other clinical features likely to be of greater discriminant value – (a) abnormal mental state or vital signs, (b) pain, (c) triggers, and (d) duration of episodes. The first half of the 'triage' approach is modeled on the pre-existing 'triage' framework used in the ED. Emergency physicians are trained to recognize patients who are acutely ill (e.g. the dizzy patient with borderline hypotension and crushing substernal chest pain who has aortic dissection). The second half of the approach (perhaps familiar to neuro-otologists, but generally unfamiliar to Emergency physicians) focuses clinical attention on specific 'triggers' and the duration of dizziness episodes, rather than on the quality of dizzy symptoms. We plan to test this new paradigm in the ED for its feasibility and effectiveness in reducing misdiagnosis of dizzy patients.

**BP5.24**
**Impulse Rotational Test: a new vestibular test**
**J. Paul Deroubaix**
*Bethune*

The Impulse rotational test (IRT) is a new vestibular test perfectly well tolerated, reproducible and characterized by a soft acceleration (20°/s2), a plateau at constant speed (20°/sec), a soft deceleration (20°/s2) followed by a pause of 10 secondes. Videonystagmography, because of its high sensitivity, is used to record this test. The interpretation of the test rests on the following elements: direct trace, cumulative eye position, number of nystagmus beats of the per-rotatory and post-rotatory phases. It is also made on average slow phase velocity, cumulative angular response and on function of transfer of energy which allows an estimation of the evolution of the slow phase velocity during per-rotatory stimulation at constant speed.

This test highlights the early signs of irritating phenomena: in these cases, vestibular prevalence is directed to pathological side and the transfer function shows that there is a maximum of gain in about 5sec. This impulse rotatory test is a method of choice for the follow-up of the patients suffering from a Ménière disease or a hydrops.

The follow-up of the peripheral vestibular deficit is done on the variation of the per and post-rotatory response: for an acute destructive syndrome, when the chair is turning toward the side of the injured ear, the per-rotatory response is weak in frequency and in speed of slow phase. At the time of the pause following immediately, a nystagmus is present whose fast phase is directed to the good ear. The evolution follows an exponential decreasing curve during the first month following the event; after the first month the regression is then of the linear type. In the central syndromes, the per-rotatory nystagmus is more frequent than in normal subjects, post-rotatory nystagmus is stronger.

All these elements show that the impulse rotatory test is fast and reliable.

**BP5.25**
**Validation of the impluse rotational test (IRT) versus caloric test**
**J. Paul Deroubaix**
*Bethune*

Material and methods. Inclusion criterion: single acute vestibular peripheral deficit: vestibular neuritis or trauma with or without translabyrinthic fracture. Exclusion criteria: acute peripheral vestibular deficit having repeated within 1 year, chronic otitis and previous of otologic surgery, Ménières disease or vestibular hydrops and vestibular neurectomy, acoustic neurinoma and neurinectomy.

There were 118 patients, 56 men and 62 women, age from 15 to 76 years. 87 patients were examined once, 27 patients were examined twice, and three were examined 3 times, for a total of 150 examinations. The time between the initial event and the initial examination was 0 day to 81 days, the time between the initial event and the last examination was 743 days.

Three types of measurement were obtained: number of nystagmic beats, velocity of slow phase, and cumulated angular response. The temporal reference corresponds to the time between the vestibular event and the registration of the data.

Criteria of analysis of the IRT: Vestibular Prévalence corresponds to the algebraic sum of the per-rotatory clockwise and counterclockwise response and the post-rotatory clockwise and counterclockwise response. Criteria of analysis of the caloric test: Vestibular preponderance corresponds to the algebraic sum of the response to cold and hot stimulations on the right and left side. The vestibular preponderance is calculated on the values of culmination. Criteria of comparison: comparison of the average and the standard deviation for each of the three types of measurement, evaluation of the ratio between

prevalence of impulse rotational test and vestibular preponderance of the caloric test according to the temporal reference for each of the three types of measurement, evaluation of the statistical regression of the prevalence of impulse rotational test and the vestibular preponderance to the caloric test according to the temporal reference for each of the three types of measurement.

Results. The time between the beginning of the vestibular event and the examination are essential for the comparative analysis of the two tests. Two of the three types of measurement are significant: velocity of the slow phase and cumulated angular response. The statistical regression of the prevalence of impulse rotational test is appreciable to the temporal reference. The regression gives an exponential decreasing curve during the first month following the event, after the first month the regression is linear. The statistical regression of the vestibular preponderance to the caloric test is linear.

Conclusion. The time between the vestibular event and the examination is essential for the analysis of impulse rotational test. The impulse rotational test is more precise than the caloric test during the first month. The correlation of the two tests is significant from the second month following the initial event. This study shows that the impulse rotational test is a significant and reliable test.

**BP5.26**

**Clinical evaluation of the otolith function using sinusoidal OVAR**

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The vestibulo-ocular reflex (VOR) generates smooth eye movements that are compensatory for head movements to ensure gaze stabilization during head rotations. The VOR consists of the semicircular-ocular reflex (ScOR) and the otolith-ocular reflex (OOR). To test the ScOR, caloric test and earth vertical axis rotational (EVAR) test are routinely used. But as for the OOR, there is no test in clinical use. The development of an assessment tool for the OOR is potentially important, because so many patients with presumed vestibular disease go undiagnosed.

Off-vertical axis rotation (OVAR) is a stimulus wherein persons are rotated while the axis about which they rotating is tilted with respect to gravity. Then the OVAR has the ability to assess the OOR. During constant velocity OVAR, only the otolith organs are stimulated while during sinusoidal rotation, both the semicircular canals and otoloth organs are stimulated. The response to sinusoidal OVAR contains a response at the fundamental and at the superimposed higher frequency components. Sinusoidal OVAR produces less nausea than constant velocity OVAR and is thus appropriate for assessing otolith function clinically.

In the present study we investigated the contributions of semicircular canal versus otolith organ signals to the VOR by providing canal-only (EVAR) and canal plus otolith 30-degree nose-down conditions (OVAR). Horizontal and vertical eye movements were recorded in eight healthy adults, ranging in age from 28 to 40 (mean 29. 5), using an infrared video recording system (2D VOG-Video-Oculography®, SensoMotolic Instruments GmbH, Berlin Germany). Stimuli were carried out sinusoidally, at 0. 2Hz, 0. 4Hz and 0. 8Hz in frequency and 60 deg/sec in maximum angular head velocity in both EVAR and OVAR.

VOR gain at 0. 2Hz was 0. 84±0. 31 (mean±S. D. ) in EVAR and 0. 77±0. 21 in OVAR, percent gain change of which resulted in 0. 6±31. 5%. VOR gain at 0. 4Hz was 0. 71±0. 16 in EVAR and 0. 61±0. 15 in OVAR, and percent gain change was 11. 5±52. 1%. All subjects showed VOR gain reduction in OVAR at 0. 8Hz (0. 73±0. 1 in EVAR and 0. 55±0. 11 in OVAR). Percent gain change was 23. 5±12. 5%. There was a significant difference of VOR gain between EVAR and OVAR at 0. 8Hz ($p<0.05$).

It was concluded that the stimulation of 0. 8Hz and 60 deg/sec in maximum angular head velocity in sinusoidal OVAR may evaluate the otolith function without discomfort for patients.

**BP5.27**

**Transtympanic versus extratympanic electro-cochleography in Meniere's disease**

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Background: Electrocochleography (ECoG) is an objective evoked response method, evaluating the cochlear electric response to acoustic stimulation. In the presence of endolymphatic hydrops (ELH) the ECoG recordings show specific changes. Most notably there is an increased summation potential (SP), a DC potential shift emanating from the outer hair cells. The increased SP is considered to be an effect of the asymmetric movement of the basilar membrane due to ELH. Thus, by being an EH detector, ECoG can valuably aid the clinical diagnosis of Meniere's disease. Transtympanic (TT) ECoG, with the active needle electrode placed on the promontory, has most often been the method of choice due to its reliability. Extratympanic (ET) ECoG, with the active electrode placed on the eardrum, is totally non-invasive but has the disadvantage of a poorer signal-to-noise ratio. Direct comparative studies of the two methods are scarce and, non-existing when it comes down to including to the most valuable variable in ELH detection, i.e. burst-evoked responses.

Aim: The aim of this study was to compare the clinical value of TT versus ET ECoG in the diagnosis of Meniere's disease.

Material and Method: ECoG recordings from 10 healthy subjects and 10 patients suffering from Meniere's disease were evaluated. Both TT and ET ECoG were carried out in the same session in all the patients/healthy subjects. The elevated absolute magnitude of the 1kHz burst-evoked SP and the increased click-evoked SP/AP ratio were used for detecting ELH.

Results: The number of successful TT ECoG registrations was 20 (100%) while the corresponding figure was 18 (90%) of the ET ECoG registrations. The poorer success rate of the ET ECoG was caused by difficulties in identifying the SP, mainly in the burst-evoked responses but also in one instance in click-evoked recordings. The upper normal limits for 1 kHz SP amplitudes and SP/AP ratios in both TT and ET ECoG were calculated based on the recordings from the healthy subjects. The number of positive measurements in the patients (exceeding the corresponding upper normal limit) using TT ECoG was 7/10, but only 3/10 using the ET method.

Conclusion: In clinical diagnosis of Meniere's

disease, transtympanic electrocochleography seems to be preferable to the extratympanic method.

**BP6.1**

**Transplantation of neural stem cells into the mouse inner ear**

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Neural stem cells have received particular attention as a material for transplantation approaches to degenerative diseases in nervous and sensory systems. However, there have been few reports on transplantation approaches for inner ear sensory systems. In this study, we examined the potential of neural stem cells as donor cells for cell therapy for inner ear disorders caused by the loss of sensory cells. Neural stem cells obtained from GFP mice were used as donor cells. We transplanted neural stem cells into the inner ear of normal mice or mice affected by aminoglycoside. The medium containing neural stem cells were injected from the second turn of cochleae or lateral semicircular canal.

Histological analysis 1-4 weeks later showed that transplant-derived cells survived in the inner ear and some of them were integrated into inner ear tissues including vestibular sensory epithelia. A major part of transplant-derived cells was localized in the perilymphatic space. Immunohistochemical analyses indicated that transplant-derived cells differentiated into neural or glial cells. In addition, transplant-derived cells that exhibited a hair cell marker was observed in vestibular epithelia damaged by aminoglycoside, although the numbers were limited.

These findings indicate that neural stem cells have potential as a material for transplantation approaches to inner ear dysfunction.

**BP6.2**

**Adaptation to Presence and Absence of Chronic Pulsatile Electrical Stimulation**

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We investigated guinea pig adaptation to constant-rate pulsatile electrical stimulation of the peripheral vestibular system. The horizontal semicircular canal in the right ear was plugged and a 150mm diameter Platinum electrode was inserted near the nerve innervating this horizontal canal. An electrical stimulation device was attached to the skull surgically. The device delivers chronic 250Hz constant-rate current pulses to the vestibular nerve via the electrode. The current pulses were biphasic with an amplitude of 80mA. The device was battery powered and portable. The animal carried the stimulator constantly and moved freely in its normal environment. When tested, the animal was restrained to be stationary in the dark, with eye position measured using a search coil.

In the first experiment, the chronic pulsatile stimulation was turned on for weeks 1,3,5,7 and off for weeks 2,4,6,8. When the electric stimulation was first turned on in weeks 1 and 3, the animal responded with a very brisk nystagmus (318 and 370 beats/min, respectively). The response decayed back toward zero gradually, taking about 24 hrs. to reduce to 13 beats/min and 11 beats/min, respectively. The responses measured during week-5 and week-7 were weaker, (peaks of 177 and 163 beats/min, respectively) and decayed rapidly (15 and 19 beats/min, respectively, in 10 minutes).

When the stimulation was first turned off during weeks 2 and 4, the nystagmus (peaks of 140 and 92 beats/min, respectively) was in the direction opposite to that observed when the stimulation was on, demonstrating an after-effect typical of central adaptation. The nystagmus decayed gradually (9 and 27 beats/min, respectively, after 24 hours), with about the same time course as when the stimulation was turned on during weeks 1 and 3. The responses measured during week-6 and week-8 were weaker (72 and 64 beats/min, respectively) and decayed very rapidly (14 and 12 beats/min, respectively after just 10 minutes).

In the second experiment, which began during the 8th week of the first experiment, stimulation was turned on in the morning of days 54, 56, 58, 62, 64 ("even days"), and turned off in the morning of days 55, 57, 61, 63, 65 ("odd days"). The day-54 response was similar to the response measured during the first day of weeks-3 and 4 described above. The responses for the following even days were much weaker and decayed even more rapidly. After 5 minutes, the direction of the nystagmus often actually reversed direction, perhaps indicative of central adaptive overcompensation. The off responses measured on the odd days were qualitatively similar to those measured on the even days but in the opposite direction.

In a control experiment, we verified that the eye response to individual biphasic pulse pairs was the same before and after chronic stimulation, showing that the efficacy of the stimulation did not change. Therefore, the measured response changes must be due to neural adaptation, presumably central, with the "learned" rapid response transitions (i. e. rapid decay rates) to the presence and absence of electrical stimulation possibly due to dual-adaptation.

**BP6.3**

**An Investigation of the Angular Vestibuloocular Reflex at Very High Frequencies Using a Prosthesis**

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We have developed a neural vestibular prosthesis to electrically stimulate the ampullary nerve in the lateral semicircular canal of animals. The prosthesis provides electrical stimulation using charge-balanced biphasic current pulses, and the modulation of the pulse rate upward and downward mimics the semicircular canal's normal signaling scheme. Head angular velocity is encoded by a proportional change in the prosthesis pulse rate, compared to the pulse rate when the subjects are stationary. Each canal receiving electrical stimulation is plugged, in order to prevent mechanical motion from confounding the prosthesis stimulation.

When head angular velocity has been communicated to the subjects via the prosthesis, compensatory eye movements have been observed, consistent with the normally functioning angular vestibuloocular reflex (AVOR). Our neural vestibular prosthesis offers the opportunity to study the AVOR at frequencies impractical

to achieve via motion. We used this opportunity to investigate the frequency response of the AVOR and characterize the gain and phase between 1 and 150 Hz.

In order to avoid confounding nonlinear effects, the prosthesis stimulation for these experiments was designed to consist of periods of stimulation at a constant stimulation rate (pulse rate) and periods of no stimulation. In other words, stimulation consisted of square waves (1 to 159 Hz) that modulated biphasic current pulses applied with a pulse rate between 50 and 5000 Hz.

Spectral results showed eye responses at frequencies that were odd harmonics of the modulating square wave. The responses at the fundamental frequency had the highest signal-to-noise ratio. Therefore, these were used to derive response gain and phase. Gain was roughly constant, within 60 percent, with no trend evident across a frequency span greater than two decades, from 1 to 150 Hz. The phase plots were incrementally linear from 1 to 150 Hz, with slopes corresponding to delays in the range from 8 to 13 msec, consistent with the known latency of the elementary AVOR. (Supported by: DC-03066)

**BP6.4**

**Vestibulo-oculomotor behavior in rats following a transient unilateral vestibular loss**

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An experimental model, using instillation of lidocaine into the middle ear cavity, offers a possibility to study awake animals in the very first period of compensation after a vestibular loss. Lidocaine causes an almost immediate functional labyrinthectomy, lasting for about one hour. During this time all the postural as well as vestibulo-oculomotor symptoms, which are related to a peripheral vestibular loss, can be demonstrated. The aim of this investigation was to evaluate vestibulo-oculomotor symptoms, during and after a transient unilateral peripheral vestibular loss in rats caused by lidocaine. The vestibulo-oculomotor reflex was assessed with or without dynamic vestibular stimulations by recordings of horizontal eye movements.

A vigorous spontaneous nystagmus (SN) was evident within 15 minutes after lidocaine instillation. The slow phase velocity (SPV) and the frequency increased rapidly to values up to 120 $^{o}$/sec and 250 - 300 beats/minute respectively, after which SN abruptly failed, as if the system overloaded. This state lasted about 40 minutes before SN reappeared with about the same frequency and SPV as during the period before the failure. Once reappeared, the SN frequency gradually abated and the gaze stabilised within approximately 10 minutes.

After recovery from the acute lidocaine effect, when SN had subsided, a reversed SPV gain asymmetry was observed during sinusoidal rotatory stimulation, i. e., a decrease in SPV gain during rotation to the contra-lidocaine side and a normal or slightly increased SPV gain during rotation to the ipsi-lidocaine side. Likewise, a reduced time constant was observed for a step stimulus towards the contra-lidocaine side whereas the time constant during stimulation towards the ipsi-lidocaine side remained normal. A similar vestibulo-oculomotor behaviour has been observed with unilateral repeated rotational stimulation causing unidirectional "habituation" (Clément, G. , Courjon, J. -H. , Jeannerod, M. & Schmid, R. (1981) Exp. Brain Res. , 42, 34-42). It has also been demonstrated that vestibular habituation is related to the cerebellar nodulus ( Cohen,H. , Cohen,B. , Raphan,T. ,WaespeW. (1992) Exp Brain Res, 90, 526-538 ).

In the present investigation, a previous nodulectomy significantly reduced the reversed gain asymmetry as observed after the shortlasting lidocain vestibular loss. This finding further support a notion that the reversed gain asymmetry is a manifestation of "vestibular habituation".

Our study shows that 1) the vestibulo-oculomotor system seems to overload shortly after a sudden vestibular loss and 2) A mechanism to counteract the pronounced asymmetry in the vestibulo-oculomotor circuitry develops during the first hour after the loss. This mechanism, which might be related to the concept of "vestibular habituation", is retained for many hours in spite of recovery of peripheral vestibular function

**BP6.5**

**5-hydroxytryptamine release in the rat medial vestibular nucleus using in vivo microdialysis**

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Anxiety or stress, is known to influence the occurrence and prognosis of vertigo and dizziness. Specifically, it has been reported that stress retards the vestibular compensation in animals with vestibular defects, suggesting that recovery from vertigo is delayed by stressful conditions. Since many studies have reported that the 5-hydroxytryptamine (5-HT) system plays an important role in the regulation of anxiety and stress, it is possible that vertigo induced by anxiety and stress may be caused by loss of control of the vestibular circuit mediated by the 5-HTergic neuronal system.

In order to clarify intrinsic characteristics of the release of 5-HT in the medial vestibular nucleus (MVN), we investigated the effect of perfusion of high KCl (100mM), calcium free Ringer's solution and a 5-HT reuptake inhibitor, clomipramine on the release of 5-HT from its nerve terminals in the MVN using in vivo microdialysis in freely moving rats. In addition, since it has been reported that somatodendritic 5-HT1A autoreceptors involve in the control of the release of 5-HT from 5-HTergic nerve endings in several brain area , we examined the regulatory role of 5-HT1A receptor in high potassium-evoked 5-HT release using the animals pretreated with the selective 5-HT1A agonist, 8-hydroxy-2-(di-n-propylamino) teralin (8-OH-DPAT).

Male Wistar rats were anesthetized with pentobarbital sodium and the skull was exposed and a microdialysis guide cannulae was stereotaxically placed into the MVN. The animals were perfused at 3&#181l/min with Ringer's solution, high potassium Ringer's solution, calcium free Ringer's solution and clomipramine (1&#181 M) for 60 min using the microdialysis probe 24 h after the implantation of guide cannulae. Animals were injected with 8-OH-DPAT (1mg/kg, i. p. ) 30 min before the perfusion of the high potassium Ringer's solution. Samples of dialysates were collected every 30 min and automatically injected into

the HPLC-ECD system for assay of extracellular 5-HT concentration.

The basal extracellular levels of 5-HT in dialysis samples from the MVN were 34. 40 ± 0. 46 fmol/90&#181 l (n=28). Depolarization with 100 mM KCl increased the 5-HT levels to about 460 &#37 of baseline in the MVN [ P < 0. 0001, n=5]. The 5-HT concentration returned to predrug levels within 30 min after reinstatement of normal Ringer's solution. The increase in release of 5-HT was inhibited by perfusion of a calcium free Ringer's solution [P < 0. 0001, n=4]. Perfusion with clomipramine produced a marked increase in 5-HT levels [P < 0. 0001, n=6]. The peak of 5-HT concentration was 60 min after the perfusion and returned to the baseline levels within 1 h after perfusion of normal Ringer's solution. 8-OH-DPAT inhibited high potassium -evoked 5-HT release in the MVN [P < 0. 005, n=5].

These findings suggest that extracellular 5-HT in the MVN is released from the nerve terminal and its regulation may be mediated by control of somatodendritic 5-HT1A receptors activation.

**BP6.6**

**Visual fixation suppression of caloric nystagmus in mutant mice deficient in delta 2 glutamate receptors**

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It is well known that the fixating mechanism of the visual system influences nystagmus of vestibular origin. Nystagmus induced by caloric stimulation in dark is reduced in light (visual suppression). And it is generally assumed that floccular Purkinje cells encodes retinal slip and controls the gain of the horizontal vestibulo-ocular reflex. Previous reports showed that lesions in the flocculus abolish visual suppression. However the precise mechanism of the visual suppression is not completely understood.

In the present study, we recorded the visual suppressions in mutant mice deficient in the delta 2 subunit of the ionotrphhic glutamate receptor (GluR delta-2) in Purkinje cells to investigate the role of glutaminergic system on the control of VOR. Wild type and homozygous mutant mice GluR delta-2 (-/-) 6-10 week old were used. The left eye was illuminated by an infrared LED and monitored by an infrared CCD camera. Eye movements were captured and analyzed by a computer. The pupil was fitted as an ellipse and the horizontal eye angular movement was calculated using the shape and direction of ellipse ( Iwashita et al 2001). Caloric stimulation was made by injection of 5-ml ice cold water into the left external ear canal in dark and light.

In wild type the slow phase velocity in dark was reduced about 90 % in light. In GluR delta-2 (-/-) mice the velocity was reduced very little (10 %), no change or even increased in light. These results suggest that the parallel fiber input to floccular Purkinje cells mediated by ionotrophic glutamate receptor play important roles in the visual suppression of the vestibular nystagmus.

**BP6.7**

**Floccular Purkinje Cell Responses During The Optokinetic Reflex In LTD-Deficient Mice**

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A longstanding but still controversial hypothesis is that long-term depression (LTD) of parallel fiber-Purkinje (P) cell synapses in the cerebellar flocculus embodies part of the neuronal information storage required for adaptation of the vestibulo-ocular reflex (VOR). Transgenic mutant mice in which LTD is blocked by P-cell specific expression of a protein kinase C (PKC) inhibitor indeed show impaired VOR adaptation, while there default eye movement performance is normal. Although these data indicate that cerebellar LTD is a prerequisite for VOR learning, they do not establish a causal link between the actual memory storage required for motor learning and cerebellar LTD. As the L7-PKCI transgene is probably activated from the early stages of P-cell differentiation, a caveat could be that P-cells cannot develop normal responsiveness to parallel-fiber and climbing-fiber inputs in the L7-PKCI mutants. If so, this could disturb any and all mechanisms of plasticity that rely either directly or indirectly on appropriate P-cell signals.

To investigate this possibility, we recorded simple spike (SS) and complex spike (CS) activity of P-cells in the flocculus of alert L7-PKCI mice and their wild type littermates during sinusoidal optokinetic stimulation (5 deg at 0. 05-0. 8 Hz). Eye movements were recorded simultaneously with the magnetic induction technique using miniature search coil implants. We found that the amplitude and phase relations of the SS and CS discharge associated with optokinetic reflex responses are very similar in wild type and mutant vertical axis (VA) P-cells. CS activity of floccular VA-cells increased with contralateral stimulus rotation and lagged ipsiversive eye velocity by ~165 deg at all test frequencies (0. 05-0. 8 Hz). SS modulation was roughly reciprocal to the CS modulation and lagged ipsiversive eye velocity by ~15 deg at all test frequencies. The spontaneous SS and CS discharge properties are also indistinguishable.

We conclude that impaired VOR learning in L7-PKCI mutants cannot be due to an overall disturbance of their floccular P-cells signals. The data thus strengthen the evidence that cerebellar LTD is necessary for short-term VOR learning, but not for the development of the normal default response patterns.

**BP6.8**

**Vestibular Decompensation in Elderly Vertigo Cases**

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After the acute stage of unilateral vestibular lesions, in most cases, vertigo and disequilibrium symptoms disappear and the equilibrium functions appear to recover by means of the vestibular compensation mechanism. Among elderly unilateral vestibular lesion patients, there are some cases in whom vertigo and disequilibrium symptoms are prolonged and difficult to treat compared to childhood or adult cases. We present these types of cases and discuss the problem of vestibular decompensation.

Case 1: 79 y/o female. She suffered from continuous

disequilibrium after Ramsay Hunt syndrome. Caloric test showed no response and horizontal rotatory nystagmus persisted.

Case 2: 72 y/o male. He complained of dizziness from 6 months previously. He experienced an episode of vestibular neuritis at 45 years of age and no vertiginous symptom had occurred since then until the present dizziness. Caloric test showed no response and horizontal rotatory nystagmus persisted. Case 3: 70 y/o male. He had experienced dizziness from 5 months previously and had a past history of vertigo in his childhood. Caloric test showed the normal response and horizontal nystagmus to the left side was persistent. MRI examination revealed hypoplasia of the left cerebellar hemisphere.

Case 1 showed a poor prognosis of unilateral vestibular lesion in an elderly patient, and the vestibular compensation mechanism did not function well. In case 2, after one vestibular compensation was functional following vestibular neuritis, it seemed to worsen due to the factors of age, diabetes mellitus, and hyperlipemia. Central vestibular compensation did not function well in elderly case 3, and disequilibrium symptoms reappeared. It is considered that case 1 showed incomplete peripheral vestibular compensation, case 2 showed peripheral vestibular decompensation, and case 3 showed central vestibular decompensation. The findings suggest that the presence of advanced age, underlying disease such as diabetes mellitus, hypertension, hyperlipemia, and neoplasms are common background factors affecting vestibular decompensation. With the expected increase in the number of aged people in the population in the near future, there may be more opportunities to encounter these kinds of cases and develop methods of treating these patients

**BP6.9**

**Subjectivvisual horizontal and stabilometer findings in unilateral severe vestibular dysfunction**

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Whereas records of a stabilometer represent body balance, subjective visual horizontal represents ocular torsion. Therefore, these tests can be used for evaluation of vestibular compensation. However, there are few reports about correlation between these two tests.

To investigate this correlation, these two tests were performed on 17 patients with unilateral severe vestibular dysfunction. In this study, 10 males and 7 females were enrolled. Causes of unilateral severe vestibular dysfunction included delayed endolymphatic hydrops in 1 patient, CP angle tumor in 5 patients, vestibular neuritis in 7 patients, Meniere's disease in 3 patients and undiagnosed internal ear damage in 1 patient.

To evaluate subjective visual horizontal we used a device that has a bar of light emitting diodes (LED). The LED bar could be rotated about the axis at its center by a subject controlling an electric motor. After the LED bar was tilted by a tester, the subject rotated the bar to the position felt horizontal with a hand controller in a completely dark room. Deviation in degree from the real horizon was measured four times and a mean value was calculated. Lengths of total track and circumferential areas with eyes open and closed were measured with a stabilometer. We evaluated the correlation between the results of subjective visual horizontal testing and those of the stabilometer testing.

No correlation was found between parameters of the stabilometer testing and deviations of subjective visual horizontal. This result has two explanations. The dissociation might be attributed to the difference of vestibular compensation in the vestibulo(otolith)-ocular reflex from that in the vestibulo-spinal reflex. Or it might be attributed to the inter-subjective difference of the contribution of the proprioceptive inputs in vestibular compensation.

**BP7.1**

**Vestibular Stimulation Alters the Equilibrium Position for Automatic Postural Responses**

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Although galvanic vestibular stimulation results in body tilt, it is not clear what role vestibular information plays in automatic postural responses that are triggered by somatosensory inputs. We investigated the vestibulospinal influence on automatic postural responses by combining galvanic vestibular stimulation with surface translations in standing subjects.

Subjects stood with eyes closed and heads turned toward the right shoulder under 3 galvanic vestibular stimulation conditions: galvanic anterior (anode on the left ear causing forward sway), galvanic posterior (cathode on the left ear causing backward sway) and no galvanic current. Just threshold vestibular stimulation (0. 2-0. 4 mA) was delivered 500 ms before, and continuously during, 3 velocities (1. 4, 4. 2, or 14 cm/s) of 9 cm backward surface translations.

Results showed that vestibular stimulation produced anterior or posterior shifts in the final CoP and CoM position that were larger during surface translations than during quiet stance. The net effect of vestibular stimulation on peak sway, after subtracting out the sway due to the surface translation, was larger for the faster, than for the slower, velocity surface translations. Vestibular stimulation also resulted in significant changes in tilt of the trunk in space that was realized by changes in the magnitude of the medium latency (91-110 ms for 4. 2 cm/s and 84-94 ms for 14 cm/s platform velocity) postural muscle responses at the ankle. The galvanic-induced changes in latency and magnitude of the first 50 ms of gastrocnemius muscle burst in response tot the backwards surface translation were consistent with changes in background muscle tone induced by the direct vestibulospinal effect of galvanic current. However, the galvanic–induced changes in the second 50 ms of the gastrocnemius response were in the opposite direction and consistent with the forward- or backward-tilted, final postural equilibrium goal. Galvanic-induced tilt was first initiated in the trunk, prior to the legs, such that changes in the gastrocnemius and soleus postural response to translations were not due to an effect of galvanic stimulation on initial ankle angle. More proximal muscles and antagonist flexors involved in the postural response were not altered by galvanic stimulation.

These results suggest that galvanic vestibulospinal stimulation can alter the central programming for the magnitude of medium latency, automatic postural responses

in ankle muscles by changing the postural equilibrium goal. The vestibular system may play a larger role in interpreting sensory reafference during postural movements, especially during fast postural movements, than in controlling quiet stance. Finally, these results indicate the vestibular system does not play a critical role in triggering the earliest postural responses but it may be critical in establishing an internal reference for verticality to permit accurate realignment of the body after a disturbance in stance equilibrium. (Supported by NIDCD CD01849. )

**BP7.2**

**Habituation to Galvanic Vestibular Stimulation Depends on Sensory Reweighting**

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We previously observed that subjects standing with eyes closed on a tilting support surface (SS) orient to the SS for small tilt amplitudes suggesting that subjects rely primarily on proprioceptive orientation cues in these conditions. However, as SS tilt amplitude increases, subjects orient more to earth vertical. This changing behavior may be explained by a reweighting of sensory orientation cues whereby the postural control system increases its reliance on vestibular cues as SS amplitude increases. If this explanation is correct, we predict that body sway evoked by galvanic vestibular stimulation (GVS) should increase with increasing SS tilt amplitude. Furthermore, if the well known habituation effect to repeated GVS is due to a central mechanism associated with sensory reweighting, we predict that habituation will decrease with increasing SS tilt as subjects rely more on vestibular information for balance control.

To test our predictions, medial-lateral (M/L) body sway was measured while subjects stood with eyes closed on a SS that tilted in a M/L direction. Test conditions included fixed SS (0 deg tilt), tilts according to a pseudorandom profile at 4 different amplitudes (1 deg , 2 deg , 4 deg , or 8 deg ), and sway-referenced SS. In each condition, a 0. 75mA pulsed bilateral, bipolar GVS was delivered through electrodes on the mastoid processes. Each test lasted about 300s, during which 6 cycles of the pseudorandom SS, 24 positive and 24 negative GVS pulses were presented. Since the pseudorandom SS stimulus was mathematically uncorrelated with the GVS stimulus, the body sway responses to the SS tilt could be analyzed separately from the GVS, and then subtracted leaving only the response to the GVS. The peak body sway amplitude in response to each GVS pulse was measured. The mean peak response provided a measure related to the vestibular contribution to postural control in each condition. The habituation to GVS was characterized by a habituation index equal to 100(Pi-Pf)/Pi, where Pi and Pf are the mean peak response in the first third and the last third of the trial, respectively.

Results showed an increasing body sway response to the GVS with increasing SS tilt amplitude. Additionally, the smallest GVS response was obtained in the fixed SS condition and the largest response in the sway-referenced SS condition. This result supports our prediction that the vestibular contribution to postural control increases with increasing SS motion. The galvanic habituation index was greatest (about 55&#37) in the fixed surface condition, decreased with increasing SS motion amplitude, and was lowest (about 5&#37) in the sway-referenced SS condition. The amount of habituation of the galvanic response was inversely correlated with the relative sensitivity to vestibular stimulation. This result supports the hypothesis that habituation of the vestibulospinal response to galvanic stimulation is a centrally mediated phenomenon associated with the sensory reweighting process. (Supported by grants NIH AG17960, DC01849, and Research Exchange Studentship from University of Bologna, Italy. )

**BP7.3**

**Postural sensory organization tests in patients with macular degeneration or glaucoma**

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This study investigates the contribution of vision to postural control in patients with central or peripheral visual field loss. Fifteen patients have been enrolled in this study so far. All patients underwent ophthalmologic, vestibular and postural control testing. Ophthalmologic examination included visual acuity and visual field tests (Goldmann and/or Humphrey automated perimetry tests). Patients were diagnosed with advanced glaucoma in both eyes (N = 6), advanced glaucoma in one eye (N = 6), advanced macular degeneration in both eyes (N = 2) and advanced macular degeneration in one eye (N = 1).

Vestibular examination included caloric, earth-vertical rotational tests and vestibular-autorotation tests. Vestibulo-ocular reflexes in response to earth-vertical axis rotation were normal in thirteen of the fifteen patients. Two patients had a slightly decreased time constant in response to a pseudorandom rotational stimulus, with one of these two patients showing decreased gains for both single sine and pseudorandom stimuli. In addition, another patient had spontaneous right-beating nystagmus.

Postural control examination consisted of sensory organization (SOT), motor control and automatic response adaptation tests (Equitest system). Patients with advanced binocular visual impairments were tested with both eyes viewing while patients with advanced monocular visual impairment were tested with both eyes viewing and with only the affected study eye viewing. All patients had normal equilibrium scores during SOT1, 2 and 3 trials, which use an earth-fixed support surface. Our analysis will therefore focus on the comparison of performances during SOT trials which use a sway-referenced support surface (SOT4: earth-fixed visual background, SOT5: eyes closed, SOT6: sway-referenced visual background).

Our preliminary analysis suggests that patients with macular degeneration (advanced central vision loss) are able to use visual inputs to improve their balance. Patients with glaucoma (advanced peripheral vision loss) show more variability in their results. Further analysis will be done to elucidate the contribution of visual inputs to postural control in these patients. This analysis will take into account the severity of the visual impairment and the vestibular contribution to postural control.

This research is supported by a NIH grant (NIH DC 00205).

**BP7.4**

**The importance of vestibular information for postural control depends on velocity of surface tilt**

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Vestibular information is known to be important for postural stability on tilting surfaces. The relative contribution of vestibular, somatosensory, and visual information to postural control when the surface tilts at different velocities is unknown.

We investigated how tilt velocity influences postural orientation and stability in 9 subjects with bilateral vestibular loss and 9 age-matched healthy subjects. Subjects stood on a force platform that tilted 6 degrees toes-up under varied velocity conditions (0. 25-32 deg/s) with and without vision. Postural responses were analyzed using kinematic, ground reaction force, and trunk and leg EMG data.

Subjects with vestibular loss were significantly more unstable than controls during surface tilts with eyes closed, but not with eyes open. Visual information effectively compensated for lack of vestibular information across a wide range of tilt velocities. With eyes closed, vestibular loss subjects were most unstable within a narrow range of tilt velocities (2-8 deg/s), losing balance in over 90% of trials under the 4 deg/s condition. Subjects did not fall during slow tilts (0. 25-1 deg/s) and fell only rarely during fast tilts (16-32 deg/s). During slow-to-medium velocity toes-up surface tilts, vestibular loss subjects leaned further backward than controls, as if trying to maintain body orientation with respect to the surface rather than to gravity. The initial, passive biomechanical response to surface tilts changed as velocity increased. Faster tilts resulted in forward, rather than backward, initial trunk pitch, providing a different combination of sensory inputs and requiring a different direction of postural response. Comparison of relative timing between trunk and ankle angles and EMG activity suggests that backward leans and falls were not caused by absence of a vestibulo-spinal reflex, but instead resulted from an active postural correction based on a misinterpretation that the body had tilted over a stable surface.

This study suggests that vestibular information contributes to interpretation of somatosensory inputs from the feet for stance control on unstable surfaces when vision is not available. Vestibular information is critical for stability during surface tilts with velocities around 4 deg/s, which are too fast for responses that depend on the slower graviceptor somatosensory system and too slow for fast somatosensory-triggered responses or passive stabilization from trunk inertia. (Support: NIDCD #DC01849 & Foundation for Physical Therapy. )

**BP7.5**

**Frequency Dependent Role of Vestibular Information for Trunk Stability**

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When subjects stand on unstable support surfaces, vestibular information becomes more important for control of posture. This study examined the frequency-dependent role of vestibular information on postural patterns while subjects stood on a support surface that translated or rotated at various frequencies.

Six subjects with profound, bilateral loss of vestibular function (VL) and 6 age-matched control subjects stood with eyes open or closed on 2 force plates during 6 frequencies of anterior/posterior surface translations (0. 1 to 1. 25 Hz at 12 cm, Study 1) or 5 frequencies of toes up/down surface rotations (. 01 to 0. 4 Hz at +1. 2 degrees, Study 2).

In Study 1, half of the VL subjects were well-compensated such that they could balance independently with eyes open at all frequencies of surface translations and showed little variation in head stability. The other half of VL subjects were poorly-compensated because they could not balance at any frequencies with eyes closed, fell often with eyes open, and showed excessive variability of head and trunk motion in space. Kinematic measures revealed two distinct postural patterns in the control subjects and the well-compensated VL subjects, a trunk stable-to-surface strategy for slow frequencies (0. 1 and 1. 25 Hz) and a trunk stable-to-gravity strategy for fast frequencies (1. 0 and 1. 25 Hz) with mixing of strategies for middle frequencies of 0. 5 and 0. 75 Hz. The poorly-compensated VL subjects could not control the trunk stable-to-gravity strategy, even with eyes open. The well-compensated subjects showed greater independence of head/trunk and hip rotation than the poorly-compensated VL subjects. All VL subjects were less stable with eyes open than age-matched controls based on variability of head and upper trunk in space and movement of the CoM (center-of-mass) over the base of support. However, leg muscle activity was normal in the vestibular loss subjects as if driven by somatosensory information from the oscillating surface. The trunk stable-in-space strategy required vestibular or visual information or large, low drift of the trunk led to falls.

In Study 2, all VL subjects could also substitute <100 grams of fingertip touch on a stationary surface for loss of vestibular information to stabilize the trunk in space. This light, nonsupportive touch reduced trunk and CoM gain and variability to control values. The VL subjects, however, were unable to control the finger in space independently of the body CoM. Vestibular, visual, and light touch information became increasingly important for postural control the faster the surface oscillations.

These results suggest that vestibular information acts as a vertical orientation reference for somatosensory control of posture and that vision and light touch can substitute for the vestibular orientation reference. Supported by NIDCD DC01849.

**BP7.6**

**Comparison of feedback modalities for vibrotactile balance prosthesis prototype**

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Objectives. To evaluate different feedback modalities with a vibrotactile balance prosthesis.

Material and methods. Six subjects, with uni- or bilateral vestibular deficit, as determined by electronystagmography and vertical axis rotation, were studied using Equitest® computerized dynamic posturography (CDP). We used sensory organization test (SOT) 5 and 6 in our study. Subjects' anterior-posterior (A/P) tilt at the waist was measured with micromechanical rate and linear accelometer. The resulting tilt estimate was displayed by a vibrotactile array attached to the torso. The vibration provided feedback to the subject which was used to control A/P sway. We have previously shown that the balance prosthesis reduces the subjects' A/P sway and improves their balance. We used four different feedback modalities:. (1) position, (2) velocity (3) the sum of position and velocity, and (4) predicted position and velocity. The subjects had earlier been taught to utilize the vibration information to maintain their balance using a modified Balance Master training task.

Results. Limited preliminary data analysis from the different feedback modalities shows that combination of position and velocity information was best feedback method, followed by information on position only. Subjects were least able to use the predictor information .

Conclusion. The best feedback modality to vibrotactile balance prosthesis is combination of position and velocity information.

**BP7.7**

**The relationship between posturography and falls in persons with vestibular disorders**

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Falls represent a common risk in patients with vestibular disorders. The sequelae of such a fall might be severe and cause significant morbidity. The purpose of this retrospective study was to determine if there was a relationship between scores on the Sensory Organization Test (SOT) of computerized dynamic posturography (CDP) and reported falls in persons with vestibular disorders. The relevant data were recorded from charts of 103 patients (64 women/39 men), evaluated and treated at the Centers for Rehabilitation Services at the University of Pittsburgh Medical Center (tertiary center). Fifty-two patients had a peripheral vestibular diagnosis, 45 had a central vestibular diagnosis, and 6 had both central and peripheral diagnoses. The ages ranged from 14-90 years (mean=60; s. d. =17). The average length of symptoms was 32 months. Patients with vestibular diagnoses were included if they had completed the SOT and the number of falls within the last 6 months was documented at the initial physical therapy evaluation. Rotational chair, caloric testing, and oculomotor test results were tabulated, if available.

The relationship between self-reported falls and falling under various conditions of the SOT was assessed with the Pearson chi-squared test, calculating odds ratios and 95% confidence intervals. Thirty percent of the patients with vestibular disorders had a history of one or more falls within the previous 6 months; 18% reported recurrent falls. Fall history was significantly associated with falling on CDP condition 6 (p = 0. 01, OR = 3. 24, 95% C. I. (1. 2-8. 5)), whereas falls on conditions 1-5 of the SOT were not related to self-reported falls. Furthermore, no correlation was found between reported falls and abnormalities on other vestibular diagnostic tests, including oculomotor, rotational chair, and caloric testing. The relationship between functional balance performance and CDP is not clearly defined in the literature. These data suggest that falls on CDP condition 6 predict a higher risk of falls in everyday life. Other vestibular diagnostic tests do not appear to predict the risk of falling in persons with vestibular dysfunction. Condition 6, in which visual and proprioceptive cues are misleading, demands the highest performance of the vestibular reflexes in maintaining upright stance.

The strong relationship between falling on condition 6 and reported falls may help clinicians better identify individuals with vestibular disorders who are at risk for falling. Intervention programs could be designed to prevent future injurious falls.

**BP7.8**

**Effects of Virtual Reality Stimulation on Postural Control**

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The effect of three virtual reality stimuli on the control of posture of 22 healthy subjects was investigated. A twisting tunnel, rotating cylinder and rotating dots were used as the stimuli. The stimuli were implemented on a PC equipped with suitable hardware and were administered using a head mounted display. Changes in postural control were evaluated using force platform posturography. It was found that the stimuli cause different reactions: the tunnel caused increased body sway following the movement of the tunnel; the cylinder and the dots caused increased body sway and displacements in the direction of the rotation. In addition, the stimuli were effective enough to cause 4 subjects to need support to keep balance. The goal of our research is the use virtual reality methods in the clinical study of posture.

**BP8.1**

**The Influence of Hypertension and Sympathetic Nerve Stimulation on Cochlear Blood Flow**

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It has been suggested that the disturbance of the microcirculation is one of the cause of sudden deafness. And the disturbance of circulation in a large blood vessel leads to cerebral infarction. A number of diseases lead to

cerebral infarction, and hypertension is one of the risk factors. It is well known that most cerebral infarctions occur early in the morning due to sympatheticotonia. We postulated that the disturbance of microcirculation in the inner ear was correlated with hypertension and sympatheticotonia.

The purpose of this study was to investigate how hypertension and sympatheticotonia affect microcirculation in the inner ear by measuring cochlear blood flow.

Materials & Methods. We used 7 Wistar Kyoto normotensive rats (WKY) as a normal control and 7 spontaneous hypertensive rats (SHR) as a hypertensive model. We made use of a probe with optic fiber separations of 0.5mm with an outer diameter of 1.0 mm connecting to a laser Doppler flowmeter. Animals were anesthetized with intraperitoneal administration of sodium pentobarbital (60mg/kg). Body temperature was monitored with a clinical thermometer inserted into the rectum and held with heating body holder to keep body temperature. Mean systemic blood pressure was measured by tail cuffing type sphygmomanometer. A ventral surgical approach was performed to expose the inner ear of the animals. The laser Doppler recording probe was placed on the basal turn of the cochlea to measure the cochlear blood flow. The coefficient of variation (CV) of cochlear blood flow was calculated and the data were analyzed statistically by Mann-Whitney's U test and Wilcoxon's signed ranks test. Mean values were considered significant at $p<0.05$.

Experiment 1 was aimed at determining the influence of hypertension on the cochlear blood flow. Cochlear blood flow was measured for 15 minutes continuously at rest both in WKY and SHR.

Experiment 2 was done to examine the influence of the sympathetic nerve stimulation on the cochlear blood flow. We adopted a cool stimulation as sympathetic nerve stimulation. An area of approximately 4°10 cm2 on the abdominal skin was cooled with a ice pack. The cochlear blood flow was measured for 15 minutes continuously in WKY.

Results. In experiment 1, the CV of cochlear blood flow at rest was significantly larger in SHR than in WKY (Mann-Whitney's U test, p=0. 0252).

In experiment 2, the following CV in the cold stimulation was significantly larger than that at rest (Wilcoxon's signed ranks test, p=0. 0180).

Discussion. In this study, the CV of the cochlear blood flow was significantly large in hypertension and in cold stimulation. We found that hypertension and sympathetic nerve stimulation disturb the inner ear microcirculation. We speculated that an unstable supply of oxygen had a potential to induce inner ear diseases such as sudden deafness.

In the future, we will investigate the relationship between sudden deafness and cerebral infarction by measuring the blood flow of the labyrinthine artery, the anterior inferior cerebellar artery and the basilar artery, which are located more centrally.

**BP8.2**

**Vestibular influence on the cardio-respiratory responses to standing up during whole body oscillation**

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Objective. To assess the influence of whole-body oscillation in the yaw plane (0. 1Hz and 0. 5 Hz) on the cardio-respiratory responses to active change of posture, from seated to standing.

Methods. Eighteen healthy subjects, age 40. 8 ± 17. 3 y. o. (body index 23. 9 ± 3. 2), and six patients with bilateral labyrinthine loss, age 54. 3 ± 4. 9 y. o. (body index 25. 6 ±1. 75) were required to stand on a platform from a seated position, after at least 10 min rest. Upon standing, the platform could either remain stationary or oscillate at 0. 1Hz or at 0. 5 Hz (20° amplitude). For two min before and 2 min after standing, head position, respiration, ECG and blood pressure were recorded at 500 Hz and analyzed offline. For comparisons, an age-matched group to the patients (53. 2 ± 13. 0 y. o. ) was selected from the healthy group.

Results. In the 2 groups: absolute changes of RR interval and blood pressure were similar for the 3 conditions. Frequency domain analysis of RR intervals showed a decrease of power spectrum density of the "respiratory" component (0. 15-0. 4 Hz) of heart rate variability on standing during the 3 conditions. The amount of decrease was related to the age of the subjects. During oscillation at 0. 5 Hz, the respiratory responses were different between groups, healthy subjects showed a significant increase of the respiratory frequency (0. 0333± 0. 048) which was not observed in the patients ($p< 0.05$, ANOVA).

Conclusion. When standing, changes of heart rate variability related to respiration are affected by age. Vestibular activation has an influence on the entrainment of respiration during movements in the yaw plane.

**BP8.3**

**Gravity Related Alteration in Blood Pressure Control in Bilabyrinthectomy Rats**

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A reference study has shown that vestibular nerve section in paralyzed anesthetized cats decreases the orthostatic reflex in the immediate postoperative phase. Recent studies in partially compensated bilabyrintectomized animals are not conclusive.

We study the effect of gravity changes on blood pressure in normal (NR) and in bilabyrinthectomized fully compensated (BR) awake rats during parabolic flights.

Blood pressure was recorded in 8 rats (dark agouti) during parabolic flight (0-G airbus A300, Novespace, France). Half of the rats were bilabyrinthectomized about three months prior to the experiment. A telemetry system was used to measure blood pressure. About 15 days prior to the experiments, a catheter was inserted into the descending abdominal aorta and a transmitter was fixed in the peritoneal cavity (TA 11PA-C40, Data Science International, St Paul, MN). Before each flight, the rats were firmly restrained in an opaque box and then mounted on the measurement setup. The head of each animal was

fixed pitched 30° nose-down so that the saccule was approximately aligned with gravitational force. Blood pressure was continuously monitored during all the flight. Measurements obtained from 20 parabolas were averaged for each rat. The data were collected for statistical analysis at the end of the stable phase of the different levels of gravity. For each parabola, 1g reference was calculated as the mean of the 5 seconds preceeding the initial 2g phase. To test the effect of gravity on blood pressure in each group, a one way repeated measures ANOVA was done followed by a Dunnett's post hoc test using 1g phases as references. To test the difference between the NR and the BR group, a t-test was performed for 2g and 0g.

Results are expressed as the difference between 2g or 0g and baseline (1g), m +/- SD. ANOVAs show a significant effect of gravity on blood pressure in NR ($p<0.001$) and in BR group ($p<0.002$). In the NR group, during hypergravity, blood pressure increased significantly (8. 7 +/- 3. 3 mmHg, $p < 0.05$) and returned to baseline level during 0g gravity. In the BR group, there was no change in blood pressure during hypergravity,but blood pressure decreased at the end of the 0g phase (-2. 2 +/- 1. 0 mmHg). Finally blood pressure in NR and BR group was significantly different in hypergravity.

This study shows that the effect of gravity on blood pressure is different in awake normal rats as compared to fully compensated bilabyrintectomized rats. It confirms that the vestibular system contributes to the blood pressure control. Implications of these results in cardiovascular control during weightlessness will be discussed.

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**BP8.4**

**Otolith effects on the cardiovascular system**

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It has been hypothesized that vestibular-cardiovascular reflexes exist to regulate blood pressure during postural changes such as occur when going from a supine to a standing position. Postural changes are detected by the semicircular canals (head rotation) and by the otolith organs (changes in head orientation with respect to gravity and linear motion). The vestibular stimulation employed in previous animal studies non-selectively activated both the semicircular canals and the otolith organs. The contribution of the otolith system has not been studied selectively.

The first experiment is to characterize cardiovascular responses to natural otolith stimulation and to gain insight into the underlying neural mechanisms, we measured heart rate (HR) and arterial blood pressure (BP) in awake rats subjected to pure linear motion in four directions: forward, backward, leftward and rightward. The linear motion consisted of an acceleration phase of 200ms (3m/s2) followed by a deceleration phase of 200ms (3m/s2). Rats were stabilized on the linear sled by a surgically implanted head holder. BP was measured using an abdominal aortic catheter chronically implanted via a femoral artery. In any of the four directions tested, transient linear motion produced short latency (about 400ms) bi-phasic responses in both HR and BP. The response in BP consists of an increasing phase (about 4s) followed by a decreasing phase (about 4s). The response in HR was the inverse of the BP response. The amplitudes of BP changes in the forward and backward directions were greater than those to the left and right. Cardiovascular responses to vestibular stimulation were not observed in pentobarbital anesthetized rats, suggesting that they are not due to body fluid movement or mechanical artifacts caused by linear acceleration.

The second experiment is to identify the region in the vestibular complex that mediates the otolith-cardiovascular reflex. Anatomical studies have found that the medial and inferior vestibular nuclei (MIVN) provide direct inputs to cardiovascular centers of the brainstem. We examined whether inactivation of the MIVN by microinjection of muscimol results in deficits in the otolith-driven BP changes. After collecting control data, rats received either unilateral or bilateral injections of muscimol hydrobromide (5 nM,180 nl), into the MIVN, through previously implanted cannulae. Twenty minutes after injections, otolith-driven BP changes were re-measured. In 2 of 4 rats receiving unilateral injections and 4 of 4 rats receiving bilateral injections, muscimol significantly reduced the otolith-driven BP changes ($p<0.05$). These results suggest that the MIVN mediate otolith-cardiovascular reflex.

**BP8.5**

**Fos Induction in the Amygdala by Hypergravity and its Relation to Motion Sickness in Rats**

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Though the vestibular periphery and the central vestibular nucleus (VN), which are confirmed to be essential for the development of motion sickness, have been investigated, neural substrates for motion sickness have not been fully determined. We have proposed that the amygdala is a candidate structure; taking into account its memory function and wide influence on behavioral, endocrine and autonomic responses. Previously, we showed that bilateral lesions of the amygdala suppressed hypergravity-induced motion sickness in rats evaluated by pica behavior as an emetic index. In the present study, using Fos expression as a marker for neural activation, we showed that vestibular information reached and activated the amygdala of rats during hypergravity stimulation.

Rats were subjected to 2G hypergravity by centrifugation for 3 hours (n=6), 24 hours (n=5), 3 days (n=4), 1 week (n=6) or 2 weeks (n=10). As a control, 6 animals were placed close to the centrifuge device to be exposed to the noise of the centrifuge for 3 hours. Six animals that had undergone bilateral labyrinthectomy were also subjected to 2G for 3 hours. All animals were sacrificed immediately after the stimulation for immunohistochemical processing except for 5 animals that were left in normal gravity for 3 hours after 2 weeks load of hypergravity to assess the effect of a negative change in gravity from 2G to 1G.

The results showed that prominent Fos expression in the central nucleus of the amygdala (CeA) was induced by hypergravity, but not by the noise alone or in the labyrinthectomized animals, and indicated vestibular input to the amygdala. The spatial pattern of Fos-positive neurons in the amygdala that are confined in the CeA was contrasted with those induced by other stressful experimental paradigms such as forced restraint,

inescapable swimming and foot shock; and suggested a vestibular specific effect on the amygdala but not a general stress reaction. Prolongation of hypergravity resulted in the reduction of Fos expression in the CeA and VN, suggesting a process of habituation. After 3 days load, the number of Fos-positive cells in the CeA was significantly less than that after 24 hours load. On the other hand, Fos induction in the VN was sustained longer to at least 3 days.

These findings suggested that adaptive changes to hypergravity in the amygdala occurred independently of changes in the VN. In addition, a return to normal gravity after 2 weeks load of hypergravity tended to reproduce Fos expression in the VN, and also in the CeA. Once adapted to the altered gravity circumstances, return to normal gravity could be provocative. Our results emphasize the importance of the amygdala in the development of motion sickness and in habituation to it.

**BP8.6**

**A "natural" independent visual background reduced simulator sickness**

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Conflicting motion and orientation cues from visual and the vestibular receptors may cause motion sickness. Previous studies indicated that an independent visual background (IVB) reduced simulator sickness (SS) and balance disturbance associated with exposure to virtual environments (VEs) and motion simulators. An IVB is a visual scene component that provides a visual reference frame congruent with the reference frame from the vestibular apparatus. Self-motion in a simulated environment is evoked by a second visual scene component that moves. A recent study showed that an IVB comprised of an earth-fixed grid was less effective in a complex driving simulator than in a simple VE. Subjects' post-experiment reports indicated that the VE motion "induced" motion of the earth-fixed grid IVB. This led to the suggestion that an IVB comprised of clouds would be less subject to induced motion and therefore would alleviate nausea more effectively than a grid IVB. Clouds are "natural" and are usually perceived as relatively stable, whereas a gird has no inherent stability.

Twelve subjects were exposed to complex motion through a cartoon-like simulated environment (Crayoland) in a driving simulator. The simulator included a full-size car, 3 video projectors, and 3 230 x 175 cm screens. Motion trajectories through Crayoland were prerecorded. In addition to the Crayoland scene, an IVB composed of 8 horizontal and 35 vertical grid lines, an IVB composed of 7 clouds, or an IVB composed of 28 clouds was presented behind the Crayoland mountains. The computer-generated images were presented as a panoramic scene and subtended a 220º horizontal field-of-regard. The scene was presented in stereo using CrystalEyes stereo glasses. Using a within-subjects experimental design, each subject was exposed to each of the 3 IVB conditions -- Grid (G); Less clouds (L); Many clouds (M). 2 subjects were randomly assigned to each of the 6 orders of IVB condition. Before and after each trial, subjects completed the Revised Simulator Sickness Questionnaire (RSSQ) and a presence / enjoyment questionnaire.

Three substantive hypotheses were examined: (1) SS would be greater for the grid IVB condition than the many clouds condition, (2) SS would be greater for the grid IVB condition than for the average of the less clouds and many clouds conditions, and (3) SS would be greater for the less clouds condition than the many clouds condition. RSSQ scores across conditions were examined using paired t-tests. Subjects reported significantly less nausea symptoms when the clouds IVB was presented versus the grid IVB.

Results from this study indicate that a "natural" IVB composed of "meaningful" objects (clouds) is more effective than a grid for alleviating SS. The data did not clearly support the suggestion that numerous clouds would be more effective than scattered ones. An IVB is among several interventions to alleviate SS in motion simulators and VEs being pursued at the Human Interface Technology Laboratory. (Supported by Eastman Kodak, Inc. and NASA Grant NCC
9-56. )

**BP8.7**

**Vestibular Regulation of Respiratory Muscle Activity: Recent Insights**

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Changes in posture can affect the resting length of respiratory pump muscles, requiring alterations in the activity of these muscles if ventilation is to be unaffected. For example, nose-up tilt of quadrupeds or standing in humans from a supine position can produce diaphragm shortening. Compensation for the effects of gravity on diaphragm length during head-up body tilts includes both an increase in diaphragm activity and a co-contraction of the abdominal muscles. The activity of some upper airway muscles also increases during certain postural alterations. This increase in activity is most evident when humans assume a supine position or quadrupeds are tilted nose-up, as under these conditions the tongue tends to shift to the back of the throat and may obstruct the airway. In particular, the tongue protruder muscle genioglossus and perhaps some pharyngeal muscles must be more active during these postural changes in order to maintain airway patency.

Considerable evidence has accumulated from experimentation in the cat and ferret to show that the vestibular system participates in eliciting posturally-related changes in respiratory muscle activity. Electrical stimulation of vestibular afferents either in reduced or awake preparations elicits changes in activity of the diaphragm, abdominal musculature, and the tongue protruder muscle genioglossus. Response latencies were 10-15 msec from stimulus onset, indicating that relatively direct neural circuits link the labyrinth with respiratory musculature. In awake animals, elimination of vestibular inputs through a bilateral labyrinthectomy produced a significant increase in spontaneous diaphragm and rectus abdominis discharges, although augmentation of rectus abdominis activity that normally occurs during nose-up body rotation was diminished. In addition, labyrinthectomy diminished the increase in genioglossal muscle activity that normally occurs during nose-up rotation of the head.

Anatomical studies using the transneuronal transport of pseudorabies virus have shown that vestibular signals likely reach respiratory motoneurons through a relay in the medial medullary reticular formation. In addition, medial medullary reticular formation neurons that expressed immunoreactivity for glutamate or the synthetic enzyme for GABA were shown to provide inputs to respiratory motoneurons, although presumed glutamatergic neurons were more prevalent. Use of isogenic strains of pseudorabies virus that could be distinguished independently demonstrated that individual medial reticular formation neurons can provide inputs to both diaphragm and abdominal motoneurons.

This evidence cumulatively shows that signals from the vestibular system impact upon the control of respiratory muscle activity, particularly during postural alterations. These findings may have significance for patients with posturally-related disturbances in respiratory muscle activity, such as obstructive apnea. (Supported by NIH grant R01 DC03732. )

**BP9.1**

**Neural Integrator - saccade generator mismatch: A possible cause of downbeat nystagmus**?

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Downbeat nystagmus is a fixation nystagmus that occurs during gaze straight ahead. Its specific cause is not known, but various hypotheses about its origin have been proposed, including a neural integrator deficit, a vestibular imbalance, or a smooth pursuit imbalance. Using the search-coil technique we recorded 3-dimensional eye movements from 19 patients with downbeat nystagmus. Patients were asked to fixate a 3x3 grid of light spots that were 18 deg apart. Horizontal, vertical, and torsional components of slow phases were transformed into Listing's coordinates. Afterward a multiple regression analysis was performed, which not only allowed the determination of "principal" dependencies (e. g. , the relationship between vertical eye velocity and vertical eye position) but also "non-principal" dependencies (e. g. , the relationship between torsional eye velocity and vertical eye position).

The following results were obtained. In addition to an integrator failure (18 of 19 patients), most patients either failed to obey Listing's law or their vertical offset showed a strong dependence on horizontal eye position. However, a good fit of the data was obtained, if one assumed a rotation of Listing's integrator coordinates with respect to the saccade generator coordinates (neural integrator - saccade generator mismatch). Thus, most patients with downbeat nystagmus had an integrator failure plus a vertical velocity offset. This offset cannot be explained by a vestibular or a smooth pursuit offset. We propose that the offset is due to a neural integrator - saccade generator mismatch, which could result from lesions to cerebellar structures or pathways to the neural integrator in the brainstem.

**BP9.2**

**The physiological basis for the generation of the quick phase of vestibular nystagmus**

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This paper reviews published evidence concerning the anatomy and physiology of excitatory and inhibitory burst neurons, pause neurons and burster driver neurons around the vestibular and abducens nuclei concerned with the generation of the quick phase of horizontal vestibular nystagmus. Available anatomical and physiological evidence, derived in the main from the work of Shimazu and his students from physiological studies in the cat, is used to show for the first time that it is possible to put together a neural network using presently known neural connections which results in the generation ofthe slow and quick phase of horizontal vestibular nystagmus during maintained horizontal angular accelerations (EBR, 2002,143:397-405).

In this paper I review the evidence and put the elements together. In a companion paper in the neural modelling session at Orcas we show that a neural network built up from these known neural connections using the modelling package GENESIS, using reasonable values for the parameters of the spiking neurons used in such a model, actually works and generates slow and quick phases of vestibular nystagmus during angular acceleration stimulation. Obviously many other connections than those shown here are also important for the generation of the quick phase but this first step integrates much isolated physiological data into a relatively simple working model onto which other connections can be integrated as they become established. This approach combines known physiology with new methods of understanding complex neural networks.

**BP9.3**

**Contribution of pontine omnipause neurons (OPN) to eye-head coordination in the cat**

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Intra-axonal staining demonstrated connections of OPNs not only with cell groups of the pontine saccade generator but also with other contingents of reticular neurons (Ohgaki et al. 1987). It was suggested that OPNs might participate in some aspects of gaze and/or head movement control. This hypothesis was indirectly supported by recordings from the so-called 'complex' OPNs (CX-OPNs) which, in contrast to typical 'saccade' OPNs, interrupt their firing for the total duration of multisaccadic gaze shifts (Petit et al. 1999). In this study we searched for anatomical and physiological evidence that would support or disprove a contribution of OPNs to eye-head coordination.

Experiments were performed on alert cats prepared for extracellular recording of OPN activity during head-free gaze shifts. Recording sessions were followed by tracing experiments aimed at anterograde labeling of OPN clusters in combination with retrograde labeling of reticulospinal neurons (RSN). Injections of HRP were made at the C2 - C3 level of the spinal cord. After recovery from anesthesia, Biocytin was injected by iontophoresis near OPN clusters identified by multi-unit spike activity. HRP and Biocytin reaction products were revealed by conventional histochemistry in serial sections through the rhombencephalon.

We reconstructed axonal trees of 10 neurons (mean diameters 24 - 38 µm) labeled by Biocytin at the sites of recording from OPN clusters. Axons of 5 cells bifurcated in ascending and descending branches (T-neurons) either on the side of the cell body or after crossing the midline. The remaining cells had unbifurcated axons that coursed rostrally through the pontine tegmentum on the ipsilateral or contralateral sides. Appositions of boutons on retrogradely labeled somata and proximal dendrites of RSNs were found on preterminal ramifications of 5 presumed OPNs. Each neuron contacted 1 - 11 RSNs (mean diameters 13 - 60 µm) located in the caudal and oral pontine reticular nuclei. Activity of 21 CX-OPNs was recorded with the head either fixed or free. When the head was fixed, their firing was interrupted during the total duration of saccade staircases, including inter- and post-saccadic slow eye movements. Timing of pauses was more variable in head-free condition. During fast head movements accompanied by a rapid succession of eye saccades, the duration of pauses was similar to the duration of combined gaze shifts. With head movements of low velocity, CX-OPNs tended to resume firing during intersaccadic intervals. The spike density during the total time of gaze movement was however lower than during gaze fixation. No correlation was found between pause duration of CX-OPNs and total duration of head movement.

Conclusion. This study revealed weak anatomical connections between OPNs and RSNs projecting to the cervical spinal cord. Examination of CX-OPN activity excluded any causal relationship between pauses in their discharges and head movements. Nevertheless, pauses encompassing several saccades and a reduced cumulative firing during combined gaze shifts had an appropriate timing to account for a disinhibition of RSNs during the early stages of head movements. The link between OPNs and RSNs can thus represent an additional, modulatory mechanism of eye-head coordination.

**BP9.4**

**Smooth pursuit eye movements in patients with bilateral vestibular loss**

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People with bilateral vestibular loss (BVL) experience unsteady gait and oscillopsia that can reduce mobility and the quality of life. Some patients adjust well to their vestibular loss and lead mostly normal lives, whereas others remain disabled. We speculated that some of the discrepancy in outcome was due to the ability of other sensory-motor systems to compensate for the vestibular loss by adaptive enhancement of their performance. Since smooth pursuit movements can help to stabilize the retinal image when the head moves, and so could partially substitute for the vestibular ocular reflex (VOR), we tested the smooth pursuit eye movements of BVL patients.

All patients were diagnosed with BVL based on VOR gains of less than 0. 5 when tested with the head impulse test. The VOR deficit was roughly symmetric in all directions (left/right, up/down and clockwise/counterclockwise). Additional diagnosis was made with caloric testing for the horizontal canals, and turntable tests for low frequency pitch head movements. The cause of BVL included auto-immune disorders and ototoxicity, but was in some cases idiopathic. Patients also completed a questionnaire to assess how their quality of life was affected by their disorder, from which we classified patients as either "well-" or "poorly adapted".

We tested patients and normal controls with predictable and unpredictable smooth pursuit targets. Three-dimensional eye movements were measured with scleral search coils. In the predictable smooth pursuit task, the target moved sinusoidally with an amplitude of 22° and the peak velocity slowly increased to 128°/s in 27s (a velocity chirp). All subjects were able to track the slowest movements of the target, but as the speed increased, saccades were substituted for smooth eye movements to track the target. Peak smooth horizontal eye velocity tended to be higher than peak smooth vertical eye velocity, and upward eye velocity tended to be higher than downward movements for all subjects. The peak smooth pursuit velocity varied widely among patients, ranging from about 20°/s to 100°/s for horizontal and 20°/s to 80°/s for vertical smooth pursuit. Subjects classified as well-adapted tended to achieve higher peak smooth pursuit velocity then poorly adapted patients. The unpredictable target task was a step-ramp stimulus with randomized direction (horizontal and vertical) and speed (10°/s, 20°/s, 40°/s and 50 °/s). At slow target speeds most patients performed similarly to the control subjects, with each showing gains near 1.

Well-adapted patients could achieve smooth pursuit gain of near 1 for even the fastest targets, whereas the poorly adapted patients and most control subjects could not. Our data suggest that the quality of smooth pursuit eye movements are correlated with positive adaptation to bilateral vestibular loss, though additional data is needed to determine if this relationship is causal. (Supported by Swiss National Science Foundation/ 3100-063669 (T. H. ) / 32-51938. 97 SCORE A (D. S. ) / 31-63465. 00 (D. S. ), Olga-Mayenfisch Foundation, Hartmann-Mueller Foundation, and Betty and David Koetser Foundation for Brain Research, Zurich, Switzerland.)

**BP9.5**

**Directional asymmetry in smooth ocular tracking in young and adult primates**

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The smooth pursuit system moves the eyes in space accurately while compensating for visual inputs from the moving background and/or vestibular inputs during head movements. As a step to understand the mechanisms underlying such interactions, we examined the influence of a stationary textured visual background on smooth tracking and compared the results in young and adult humans and monkeys.

Six humans (3 children, 3 adults) and 6 macaque monkeys (5 young, one adult) were used. Human eye

movements were recorded using infrared oculography and evoked by a sinusoidally moving target presented on a computer monitor. Scleral search coils were used for monkeys while they tracked a target presented on a tangent screen by back-projection. In 2 of the 5 young monkeys, a computer monitor was also used to present identical visual stimuli in order to compare the results in both species. The target moved in a sinusoidal or trapezoidal fashion with or without whole body rotation in the same plane. Two kinds of backgrounds, homogeneous and stationary textured, were used. Eye gains were calculated in each condition to compare the influence of the textured background.

Children showed asymmetric eye movements during vertical pursuit across the textured (but not homogenous) background; upward pursuit was severely impaired, and consisted mostly of catch-up-saccades. In contrast, adults showed no asymmetry during pursuit across the different types of background. Monkeys behaved similarly; only slight effects were observed with the textured background in a mature monkey, whereas upward pursuit was severely impaired in young monkeys. In addition, cancellation of the vestibulo-ocular reflex (VOR) was severely impaired during upward eye and head movements, resulting in residual downward VOR in young monkeys.

Our results indicate the existence of the directional asymmetry in smooth ocular tracking in the presence of visual background in young and adult primate. We suggest that this asymmetry may reflect a different neural organization of the vertical, particularly upward, pursuit system in the face of conflicting visual and vestibular inputs that can be associated with pursuit eye movements. Apparently, proper compensation matures late.

**BP9.6**

**Eye-, head- and gaze-movement during horizontal and vertical gaze pursuit in SCA6**

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In daily life, we obtain visual information from slowly moving objects using coordinated movements of eyes and head. Lanman et al. (1978) suggested that such gaze (eye+head) pursuit is produced by a common drive that interacts with the vestibular system to override the vestibulo-ocular reflex (VOR). Neural recording (Lisberger et al. 1978, Suzuki et al. 1988) and lesion studies (Zee et al. 1981, Robinson et al. 1997) in monkeys have implicated the cerebellum in control of smooth eye movements but less is known about gaze pursuit with head unrestrained.

To clarify the role of cerebellum in coordination of eye and head movements, we studied smooth gaze tracking with head restrained and unrestrained in patients with an autosomal dominant pure cerebellar ataxia (SCA6).

Six SCA6 patients participated in this study and their results were compared with those of age-matched normal controls. Subjects sat on a chair facing a vertical screen. Chair rotation was applied only horizontally. Laser spot target and/or chair were moved sinusoidally at 0. 2 or 0. 5 Hz (±10°). Subjects tracked the target either with head free or head restrained to the chair. Infrared oculography was used to record horizontal and vertical eye movements. Subjects wore a helmet to which a search coil was attached to record horizontal and vertical head movements. A small laser projector (i. e. head laser) was also attached to the helmet to give subjects visual feedback of head position.

Three tasks were tested with head restrained: smooth pursuit, VOR-cancellation and VOR in darkness. During VOR cancellation, a chair-fixed laser projector was used to present a target that moved in-phase with the chair with the same direction and amplitude. During head free pursuit, subjects were asked to track the target under three different head motion conditions; 1) to track the target in their most comfortable way (comfortable task); 2) to pursue the target spot with the head-laser spot (head-laser task); and 3) to track the target mainly using head movement (use-head task). Eye-, head-, gaze- gain and phase shifts relative to stimulus velocity were calculated in each task.

All SCA6 patients showed severe impairment of smooth pursuit. The most severely effected patients also had difficulty with VOR cancellation but this deficit was not significant across the population. Neither normals nor patients used large head movements to track the ±10° target motion in the comfortable condition even though this meant that patients employed saccadic eye tracking. During head free pursuit with the head-laser and use-head conditions, patients showed high head-gains (mean 1. 08) which were opposed by backward eye movements (mean 0. 41) resulting in smooth gaze movements too small to stabilize the target. Normals never exhibited such opposing eye-head movements in the head laser task but some did so in the use head task. In either case, the summed gaze movements were close to target velocity.

These results suggest that cerebellar dysfunction in SCA6 did not impair smooth head tracking itself but did impair gaze tracking through disordered eye-head coordination.

**BP9.7**

**Volitional control of smooth pursuit and its role in predictive pursuit of target motion sequences**

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When subjects view repeated, constant velocity stimuli (ramps), each preceded by an audio warning cue at a fixed time before target onset, anticipatory smooth pursuit eye movements build up prior to target onset. We have now used this 'remembered pursuit' technique to examine anticipatory responses to sequences composed of four ramps, each ramp being presented for 400ms with an interval of 200ms between ramps. Multiple sequences were formed by using differing combinations of target velocities for each ramp in the sequence. Velocities of 15 or 30deg/s to left or right could be used for any of the ramp components within a single sequence. Each multi-ramp sequence was presented at least 6 times. Responses to 4-ramp stimuli were then compared with responses to single ramps of comparable velocity.

Even within the second presentation of a new

sequence, anticipatory eye movements were evident prior to onset of each ramp component and predictive responses to many different, complex patterns of smooth eye movement were rapidly learned in this way. Anticipatory eye velocity (measured 100ms after target onset, prior to visual feedback) increased with increasing target velocity for all ramp components within a sequence. In general, the results showed that the response to 4-ramp sequences could be represented by the concatenation of anticipatory responses to each of the individual ramp components.

To test whether the response to each ramp component was pre-programmed we introduced unexpected changes into single ramp components of the 4-ramp sequences. Whichever ramp was changed, the initial eye velocity trajectory continued to be identical to that of the response to the previous sequence for at least 150ms after the change, even though it was inappropriate for the newly modified target velocity. The results suggest that subjects store speed, direction and timing information about each ramp individually and make a pre-programmed response to each component of a multi-ramp sequence in turn.

In a second experiment we investigated whether subjects could use stored information to exert volitional control over anticipatory smooth pursuit even when movement speed and direction were randomised. To this end, each target presentation was preceded by a stationary symbolic cue indicating the speed and direction of upcoming target motion. Motion stimuli were single ramps of duration 400ms and speed 10-40 deg/s to left or right, starting at centre.

Following a single practice trial to allow the association of symbolic cues with target velocity, subjects could use the cues to both select the direction and grade the speed of anticipatory smooth movements. Moreover, the anticipatory velocity (100ms after target onset) was not significantly less than for a control condition in which target motion was not randomised.

The results of the two experiments indicate that subjects can rapidly store information sufficient to reproduce a sequence of anticipatory responses for the tracking of a relatively complex target motion stimulus. Such anticipatory responses may be based on a pre-learned sequence or they may be initiated on the basis of cognitive cues, which, in natural conditions, could include perceived future changes of direction or speed.

**BP9.8**

**Human responses to vestibular and visual stimuli moving in depth: similarities and differences**

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Visual stabilization in response to head rotations is achieved by the synergistic cooperation of the angular vestibular and optokinetic reflexes (Robinson, 1977). An hypothesis for a similar organization of the translational VOR and the smooth pursuit system was suggested in monkeys (Busettini et al. , 1991). Visual stabilization during fore/aft translations and ocular following of targets moving in depth requires eye movements that depend dramatically upon the eccentricity of the object of interest with respect to the eyes. Here we set out to investigate binocular coordination in response to vestibular and visual stimuli calling for comparable eye movements moving the point of regard in depth.

We recorded the responses evoked by small (about 3 cm) fore/aft abrupt (about 0. 7g) translations in four normal subjects while viewing a near target. In the forward and backward starting positions the target was 15 or 10. 5 cm away respectively. Three repetitions were recorded for each subject: target centered between the eyes and target aligned with each eye (Müller). In a second set of experiments we used mean translation profile computed for each subject to drive a visual stimulus across the same distances and in the same eccentricities used during translations.

The responses differed mostly when the targets were centered between the eyes with fewer and later saccadic corrections during surges. Combined saccade-vergence movements were systematically observed in the Müller setup for both pursuit and t-VOR. The response latency in surges (65±28 and 33±12 ms for convergence and divergence), was significantly lower ($P<0.001$) than during pursuit (126±28 and 95±49 ms for convergence and divergence). Peak eye velocity was lower in 3 subjects ($P<0.05$ during pursuit but was reached at similar times when compensating for the different latencies. The dynamics of the response were those of a high-pass system for t-VOR while low-pass, possibly complementary behavior was shown by the pursuit response.

**BP9.9**

**Video-Oculography in the Gerbil**

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Vestibulo-ocular and optokinetic reflexes (VOR and OKR) and pupil diameter were measured in young adult gerbils using infrared video-oculography during head-fixed binocular recordings. We evaluated both single-beam retinal reflection, and the more standard pupillary light-sink technique, preferring the later. Eye movements were generally conjugate with occasional spontaneous movements, and independent drifting movements in the dark. The horizontal optokinetic response to sinusoidal motion of a randomly spaced white dot pattern was maximal near zero deg/sec, stronger temporonasally, and dropped off quickly at ~20 deg/sec. Constant velocity gain was near unity through 60-80 deg/sec with a sharp drop-off. Monocular viewing revealed almost no nasotemporal optokinetic response. Pupil diameter was found to correlate positively with optokinetic gain, but also have a circadian rhythm (smaller at dusk) that related inversely to VOR gain.

Gerbils were able to suppress their optokinetic response for long periods, which resumed after a vestibular stimulus. The horizontal angular VOR gain was relatively flat across 0. 1 to 1. 0 Hz (phase near zero), with a mean gain of ~0. 78 in the dark, and 1. 0 with the fixed pattern surround (N=15). Most animals also revealed a strong slow phase eye velocity asymmetry (temporonasal dominance) in the half-cycle gain of their horizontal angular VOR response in the dark. A constant velocity horizontal optokinetic bias velocity did not change the gain or symmetry of the sinusoidal VOR response, but shifted the directional velocity and phase of the response proportional to the bias velocity. Both cross-coupling (pitch or roll while rotating) and pseudo-OVAR (off-vertical axis rotation) stimuli generated horizontal nystagmus.

The findings suggest that the gerbil, like other lateral-eyed rodents, relies on otolith cues to interpret angular motion.

**BP9.10**
**Measurement of the Movements of Many Bones in Many Directions with an Eye Movement Monitor**
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The electromagnetic eye movement monitor is the most accurate method to measure eye movements. A coil of wire is embedded in a contact lens for humans, or surgically implanted around the eye ball for animals. This coil is called a "search coil", because it can be moved around to determine the strength and direction of an alternating magnetic field. The subject is put inside three magnetic fields, one left-right (X), one up-down (Y), and one front-back (Z). The fields oscillate at 48, 60 and Z = 80 KHz. These fields induce voltages in the search coil, which change with rotations. The three frequencies are separated by lock-in amplifiers.

Three fields, not two, are necessary to measure the coil direction at all possible angles. Investigators have traditionally put the coil close to the center of two Helmholtz field coils, where the field is uniform. This is not necessary. All that is required is that the field be known at the coil location. With our square coils, the field everywhere can be obtained as an analytical expression, by integrating the Biot and Savart law.

Suppose that arm movements are to be measured. The center of the field coils is (0,0,0). The subject shoulder is fixated, and the location (x,y,z) of the center of rotation of the shoulder ball-and-socket joint is measured.

Two search coils of 2 cm diameter and 10 turns, are fastened to the upper arm so that they are approximately perpendicular. These coils must be attached to the humerus (e. g. , with pins), so that the coils move with the bone, and do not slide around with the skin. (A good place is at the elbow, where no muscle covers the humerus. ) The humerus is a rigid body; a rigid body requires 3 angles to specify its orientation in space. One coil can only measure 2 angles. Thus there must be 2 coils on each bone.

The X, Y and Z output signals for all search coils are measured. Then the equations for the B field everywhere, and the constraint that the humerus rotate inside its socket, can be solved to uniquely determine the 3 angles of orientation.

Next the humerus is measured, so that the location (x,y,z) of the center of rotation of the elbow hinge joint is known. Two more search coils are rigidly attached to the ulna at the wrist. The orientation of the forearm can thus be determined. Next can come the wrist and fingers.

Thus the locations of the whole arm, the head and eyes, and other body parts can be measured in three dimensions, with high precision, low noise, low drift, and at millisecond intervals during voluntary and vestibularly-induced movements.

**BP10.1**
**Decreased blood pressure activates the peripheral vestibular receptors in rats**
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The vestibular system controls posture and movement by vestibuloocular and vestibulospinal reflexes. In this study, the response of peripheral vestibular receptors in acute hypotension was investigated in anesthetized Sprague-Dawley rats. Changes of cFos-like (cFL) protein expression in the medial vestibular nuclei (MVN) and electrical activity in MVN and afferent vestibular nerve were measured following acute hypotension induced by either intravenous infusion of sodium nitroprusside, or hemorrhage.

Expression of cFL protein was observed in bilateral superior, medial, and spinal vestibular nuclei except lateral vestibular nucleus after the induction of acute hypotension in control animals with intact labyrinth. Acute hypotension in unilateral labyrinthectomized rats produced expression of cFL protein in contralateral vestibular nuclei to the lesion but not in ipsilateral. However, cFL protein was not expressed in bilateral vestibular nuclei after the induction of acute hypotension in bilateral labyrinthectomized animals. In electrical activity of animals with intact labyrinths, acute hypotension produced excitation in two-thirds of type I neurons and inhibition in two-thirds of type II neurons recorded in MVN. In unilaterally labyrinthectomized animals, two-thirds of type I neurons ipsilateral to the lesion showed an inhibitory response, and two-thirds of contralateral type I neurons showed an excitatory response after the induction of acute hypotension. The response patterns of type II neurons were opposite those of type I neurons. In the afferent vestibular nerve, spontaneous activity and gain obtained by sinusoidal rotation of the whole body were increased after the induction of acute hypotension. Increased spontaneous activity of the vestibular nerve following acute hypotension was abolished by pretreatment of kynurenic acid, NMDA antagonist of glutamate.

These results suggest that decreased blood flow in the peripheral vestibular receptors increased activity of the hair cells by excitotoxicity and then the vestibular system plays a significant role in control of blood pressure through feedback system in physiological range. (Supported by Brain Science Research M1-0108-00-0001)

**BP10.2**
**Acetyl-DL-Leucine Effects on Vestibular Neurons Explains its Efficacy During Vertigo Crisis**
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For more than 40 years, high doses of acetyl-DL-leucine (Tanganil®) have been successfully used in clinical practice to treat acute vertigo crises without generating strong side effects. However, the mechanisms underlying this action of acetyl-DL-leucine are still unknown. Acetyl-DL-leucine was shown to accelerate behavioral compensation following unilateral labyrinthectomy in cats, but has only minor effects on normal vestibular function in humans.

The effects of acetyl-DL-leucine on central vestibular neurons (VNn) were first assessed in brainstem slices taken from normal guinea pigs. Only moderate

effects were obtained using concentrations similar to those reached in the blood in clinical practice. However, we could demonstrate that acetyl-DL-leucine had significant depolarizing effects on the VNn that had a more hyperpolarized than normal mean membrane potential, and significant hyperpolarizing effects on the neurons with a more depolarized than normal membrane potential. Altogether, acetyl-DL-leucine tended to bring back all VNn towards a normal mean membrane potential of about – 60 mV.

To check this hypothesis, we compared the effects of acetyl-DL-leucine obtained on isolated, in vitro whole brains (IWBs) taken from normal animals with those obtained on IWBs taken from previously labyrinthectomized animals. In control IWBs, the level of activity and membrane potential of VNn is similar on both sides of the brainstem, with a mean membrane potential value close to – 60 mV. In contrast, the level of activity of VNn is highly asymmetric between both sides of the brainstem on IWBs taken from previously labyrinthectomized animals (Vibert et al. 1999, Neuroscience 93: 413-432). In accordance with our hypothesis, acetyl-DL-leucine had only moderate effects on IWBs taken from normal animals, but strongly reduced the asymmetry characterizing the vestibular-related networks of IWBs taken from previously labyrinthectomized animals. Acetyl-DL-leucine acted mainly by inhibiting the abnormally depolarized neurons on the hyperactive side, but tended also to activate the abnormally hyperpolarized neurons on the hypoactive side.

In a last step, we undertook an in vivo study to quantify the effect of acetyl-leucine on vestibular compensation in the guinea pig. Administration of acetyl-DL-leucine induced a significant decrease of the spontaneous ocular nystagmus and horizontal head deviation induced by unilateral labyrinthectomy, beginning in the first few hours of compensation. The effect of the drug was maximal in the second and third days following the lesion.

Altogether, acetyl-DL-leucine seems to act almost exclusively on abnormally polarized central vestibular neurons by bringing back their membrane potential towards its normal value close to -60 mV. Since in animal models, acute vestibular disorders are associated with strong asymmetries in central vestibular networks, these data suggest how acetyl-DL-leucine could reduce vestibular-related imbalances in humans. Indeed, acetyl-DL-leucine would at the same time activate the hypoactive VNn on the lesioned side and suppress the hyperactivity of VNn on the contralesional side, thus strongly reducing the imbalance between the activity of central vestibular networks on both sides of the brainstem.

**BP10.3**

**Central Primary Vestibular Afferent Projections in the Gerbil**

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Examination of the central distribution of terminals following labeling of the individual subdivisions of the vestibular nerve reveals areas where otolith and canal afferent terminate. This study examines the central projections of the vestibular nerve in the gerbil with an emphasis on areas where canal and otolith inputs overlap and where vestibular inputs overlap with other sensory signals. This study also correlates the location of projection neurons (vestibulo-ocular and vestibulo-spinal) with density of afferent input.

Tracers, horseradish peroxidase (HRP) and biotinylated dextran amine (BDA), were injected directly into the neuroepithelium of one semicircular canal ampulla or otolith organ in a gerbil. The animals were sacrificed and tissue reacted according to well-established protocols. Adjacent end organs were inspected for spread of the injection beyond the desired target. A total of 80 gerbils (at least 14 for each end-organ) were successfully injected, processed, and analyzed. Some results have been reported previously.

Overlap of saccular and canal projections areas are scant. Saccular projections are strongest laterally, especially in the descending nucleus and nucleus y, which have little canal input. Utricular projections terminate in most of the vestibular nuclei and thereby overlap with input from all semicircular canals. This overlap is primarily in the rostral and medial parts of the medial vestibular nucleus with lateral and anterior canal afferents and the ventral-lateral portion of the lateral nucleus with lateral canal afferents. Utricular projections to the superior vestibular nucleus are weaker, but also overlap canal projections. All five subdivisions projected to the granular cell layer of the uvula.

Opportunity for multisensory integration also exists with saccular projections to the cochlear nuclei, utricular and saccular projections to the external cuneate, and lateral canal projections to the nucleus prepositus. Results in the gerbil are similar to results reported for the squirrel monkey and pigeon. (Supported by NIH R01-DC04070, R01-DC00385, KO8-DC00182. )

**BP10.4**

**Induction of Immediate-Early Gene Products in Vestibular Nuclear Complex by AICA Occlusion in Rats**

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The purpose of this study was to evaluate expression of immediate-early gene products, metabolic markers of neural excitation in neuronal cells, in the vestibular nuclear complex by occlusion of anterior inferior cerebellar artery(AICA) in adult Sprague-Dalwey rats. After chloral hydrate anesthesia all animals were received unilateral occlusion of AICA by using microsurgical clamp for 30 min to induce temporally ischemia in brain stem and inner ear. Immunohistochemical staining and image analysis for cFos, FosB, Krox-24, and JunB proteins were performed 2 hours after occlusion of AICA.

There was high expression of cFos protein in bilateral medial medial and inferior vestibular nuclei 2 hours after unilateral occlusion of AICA. But AICA occlusion induced minimal change in cFos expression in lateral and superior vestibular nuclei. Mild to moderate expression of FosB and

Jun B protein was observed 2 hour ischemic injury in brain stem and inner ear. A few neurons in vestibular complex showed immunoreactivity for Krox-24 protein following AICA occlusion. Furthermore pretreatment of bilateral labyrinthectomy resulted in significant reduction of immunoreactivity for cFos, FosB, and JunB proteins in medial and vesitbular expressions 2 hours after unilateral occlusion of AICA.

These results suggest that ischemia of peripheral vestibular apparatus plays a major role in expression of immediate-early gene products in medial and inferior vestibular nuclei of rats.

**BP10.5**

**VOR Dynamics During High Frequency and Velocity Rotations: Behavioral Versus Neuronal Responses**

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The vestibulo-ocular reflex (VOR) and neural encoding of VOR eye movements has been primarily studied using passive head rotations at low velocity (< 50 Hz) and frequencies (< 5 Hz). Recent studies in humans have shown that, primates generate head movements that reach velocities as high as 200-500 deg/s and contain frequency components up to 20Hz. Here we evaluated VOR signal processing, at the levels of ocular behaviour and pathway circuitry, by applying high-frequency and high velocity oscillations of the head on the body of three rhesus monkeys.

First the VOR was characterized during high frequency rotations. A torque motor assembly was used to apply passive rotations over a wide frequency range (5 - 26 Hz). Monkeys were first rotated at ±50deg/s, while they viewed earth stationary targets in the light and in the dark. For two monkeys, the gain of evoked eye movements typically remained constant across all frequencies (P>0. 15), having values near unity. The gain of the third monkey's VOR was qualitatively similar, but increased slightly as a function of frequency. For all three animals, the phase of the VOR was much more compensatory across the frequencies tested than predicted by a 7 ms latency. For example, we observed a 5 deg rather than a 70 deg phase lag at 26 Hz. We next oscillated the head at peak velocities greater than ±50 deg /s (~100-300 deg/s). The VOR gain and phase remained relatively constant at a given frequency for a wide range (from ±50 deg /s to approximately ±300 deg/s) of rotational head velocities. Finally, to determine the minimal latency of the VOR, we applied transient (20 - 30ms) perturbations with much greater accelerations (>15,000 deg /s2 ) than have been previously employed. Our results indicate that the rotational VOR latency is as short as 5 ms.

We next addressed the question of how signal processing, at the level of pathway circuitry and single neuron responses, determine VOR response dynamics. The efficacy of the direct VOR pathways during high velocity head rotations was measured by recording from individual vestibular nuclei neurons while the monkeys head was passively rotated. For head rotations in a neuron's off-direction, neuronal cut-off occurred at velocities far less than those generated during our daily activities (100 - 200 deg/s). For head rotations in the on-direction, we observed a significant soft saturation for most neurons for velocities > 200 deg/s. Moreover, individual neurons began to reach their maximal firing rates at velocities > 300 deg/s. Remarkably, the concurrently measured VOR remained compensatory for head rotations up to 400 deg. We propose that the non-linear dynamics of VOR pathways are offset by the complementary dynamics of the oculomotor plant (Sylvestre and Cullen 1999), thereby ensuring that the VOR remains linear over a wide range of velocities.

Subjects were tested in the dark for 8 initial orientations and 2 rotation directions (clockwise [CW]; counterclockwise [CCW]). Using a somatosensory bar, we measured subjective tilts with respect to earth-vertical during (B). Using video cameras, we measured VOR eye movements during (C). For both directions of rotation, the horizontal VOR was significantly larger for FC than for BC, and significantly larger for BM than for FM. We separated putative estimates of the angular and linear VOR components from the total VOR by comparing VOR responses for orientations separated by 180deg. The putative linear VOR varied sinusoidally with subject orientation (CW: Amplitude=8. 2deg/s and Phase=133. 9deg; CCW : Amplitude=11. 1deg/s and Phase=52. 1deg), matching predictions. These results agree with the hypothesis that a linear VOR compensatory for an estimate of inter-aural linear acceleration, dependent on subject orientation, superimposes on the angular VOR, which is relatively independent of subject orientation. (Supported by NIDCD grant DC04644. )

**BP10.6**

**Convergence of somatosensory inputs to the vestibular nuclei of labyrinthectomized and intact cats**

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It is well established that nonlabyrinthine inputs influence the activity of vestibular nucleus neurons. For example, the integration of signals from the labyrinth and neck by these neurons presumably provides for the discrimination of whole body from head on body movements (Wilson and Melvill Jones 1979). Besides inputs from the neck, both anatomical (McKelvey et al. 1989) and physiological (Fredrickson et al. 1966; Wilson et al. 1966a; 1966b; Barnes and Pompeiano 1971; Pompeiano 1972; Rubin et al. 1977; 1979; D'Ascanio et al. 1986; Kasper et al. 1986) studies have also demonstrated that the vestibular nuclei receive afferent signals from the entire length of the spinal cord.

Although the functional significance of limb and visceral inputs to the vestibular nuclei remains largely unknown, these signals presumably provide for a more precise, unambiguous determination of body position in space than is available from consideration of vestibular inputs alone. The major goal of this study was to determine the patterns of convergence of nonlabyrinthine inputs from the limbs and viscera onto vestibular nucleus neurons receiving signals from vertical semicircular canals or otolith organs. A secondary aim was to ascertain whether the effects of nonlabyrinthine inputs on the activity of vestibular nucleus neurons is affected by bilateral peripheral vestibular lesions.

The majority (72%) of vestibular nucleus neurons in labyrinth-intact animals whose firing was modulated by vertical rotations responded to electrical stimulation of limb

and/or visceral nerves; the activity of even more vestibular nucleus neurons (93%) was affected by limb or visceral nerve stimulation in chronically labyrinthectomized preparations. Some neurons received nonlabyrinthine inputs from a variety of peripheral sources, including antagonist muscles acting at the same joint, whereas others received inputs from more limited sources. Furthermore, we showed that vagus nerve stimulation alters the firing rate of vestibular nucleus neurons, thereby supporting the hypothesis that visceral inputs modulate physiological processes mediated by the central vestibular system (Mittelstaedt 1996; Mittelstaedt and Mittelstaedt 1996)

These data suggest that nonlabyrinthine inputs elicited during movement will modulate the processing of information by the central vestibular system, and may contribute to the recovery of spontaneous activity of vestibular nucleus neurons following peripheral vestibular lesions. In combination, the present data support the notion that whole-body movements in vertical planes elicit a variety of sensory inputs that are integrated by the central vestibular system. (Supported by NIH Grant R01-DC00693. Brian J. Jian supported by NASA Graduate Student Research Stipend)

**BP10.7**

**Postnatal development of synaptic plasticity in the rat medial vestibular nuclei**

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In brain stem slices from adult rats (> P28), long term potentiation (LTP) can be consistently induced in the ventral part of the medial vestibular nuclei (vMVN) by high frequency stimulation (HFS) of the primary vestibular afferents and by exogenous glutamate. NMDA receptors (NMDARs) are involved in mediating the induction of LTP, whereas metabotropic glutamate receptors (mGluRs) may facilitate or inhibit it. In fact, the full expression of LTP depends on mGluRs1 activation, which is impeded by mGluR5. In addition, presynaptic mGluR2/R3 controlling glutamate release, prevent LTP induction during normal synaptic transmission.

Immunoblot and immunocytochemical studies have recently shown postnatal developmental changes in the expression of NMDAR subunits (NR2A-C) and mGluR subtypes in vestibular nuclei. In fact, the expression of NR2s and mGluR1 increases from birth to adult stage (P28) while that of mGluRs5 decreases. In addition mGluR2/R3 show a peak of expression at P7, and then their expression decays during the following week. According to this receptor development it may be predicted that vestibular synaptic plasticity changes during the first postnatal weeks and the full induction of LTP may only occur when the facilitatory receptors are fully expressed. Therefore, in brain stem slices from P7 to P28 rats we investigated the effects of HFS and Glutamate infusion (100 06DM) on the amplitude of the field potential N1 wave in the vMVN.

HFS and Glutamate induced long term depression (LTD) in about 50% of the cases and LTP in 10% of the cases during P7-P9. After P9 LTD was no longer induced, while the probability of eliciting LTP increased to reach the adult value (75%) at about P21. The change in the LTP occurrence was particularly evident between P12 and P18 and, during this transitional period, the time course of the LTP induction was significantly slower than that in the adult stage. These findings suggest that LTP is prevented during the early period after birth when the inhibitory receptors are prevailing over the facilitatory ones, but, when the reverse of this prevalence takes place, the probability of inducing LTP significantly increases.

**BP10.8**

**Nonlinearity in canal interactions during yaw rotation in humans with unilateral vestibular loss**

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High acceleration yaw rotation is known to produce marked asymmetry in the unilaterally deafferented human horizontal vestibulo-ocular reflex VOR, attributed to non-linearity in hair cell or primary afferent neuron response. In the current study, the VOR was studied by canal planes in humans with unilateral vestibular deafferentation.

Eleven unilaterally deafferented adults were studied in response to transient, direction randomized, whole body yaw acceleration at 2800 deg/s2. Immediately prior to rotation subjects viewed targets at 15 cm or 500 cm. Rotation was about vertical (yaw) axes 10 cm anterior to the eyes, between the eyes, between the vestibular organs, and 13 cm posterior to the vestibular organs. Eye and head positions were measured in 3-D with dual-winding magnetic search coil s.

The rotational axis delivered most of the stimulus to the horizontal canal (HC). During the 50 ms period beginning 100 ms after head rotation onset, velocity in the HC plane averaged 104 ± 4 deg/s (mean ± SE), and velocity in both the anterior (AC) and posterior (PC) canal planes averaged 13 ± 6 deg/s. Gain was calculated for each canal by dividing eye velocity by head velocity for the respective components in the specific plane. It was often the case that head velocity in the plane of the canal was too low to calculate an accurate gain. Gain in the HC plane has been reported previously and is strongly dependent on target distance and the location of the rotational axis. Contralesional HC plane gain was 0. 56 ± 0. 03; ipsilesional gain was significantly lower at 0. 37 ± 0. 03 when averaged across target distances and rotational axes. Gains in the AC and PC planes were independent of target distance and rotational axis. Contralesional AC plane gain was 0. 52 ± 0. 13, while ipsilesional gain was significantly lower at 0. 17 ± 0. 11. Contralesional PC plane gain was 0. 34 ± 0. 10, not significantly different from the ipsilesional gain of 0. 21 ± 0. 16 (p = 0. 22).

These results indicate existence of a significant directional asymmetry in the AC plane even at the relatively low stimulus component of 13 deg/s, one that dose not produce significant asymmetry when delivered in isolation to the HC. The asymmetric AC response may be related to concurrent saturation in the HC pathway. Since the coordinate system defined by the canals differs from that of the extra ocular muscles, there is likely to be convergence of inputs from each of the canals. The AC plane asymmetry may be caused by saturation in common pathways by the intense stimulus in the HC.

**BP11.1**

**Disconjugate Surge Linear Vestibulo-ocular Reflex**

**(LVOR) with Horizontally Eccentric Targets**

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Visual fixation during anteroposterior head translation (surge) requires an LVOR that depends both on target direction and target distance, and potentially differing in the two eyes. We subjected normal and unilaterally vestibularly deafferented (UVD) humans to transient surge while viewing horizontally displaced targets to evoke a horizontal surge LVOR.

Transients of 0. 5 G peak whole body surge acceleration were delivered by a pneumatic servo on which were seated 9 normal adults (mean age 28±2 yrs, mean ± SE) and 7 subjects (mean age 60±4 yrs) with chronic UVD by labyrinthectomy or neurectomy. Eye rotation was sampled at 1,200 Hz using a dual winding search coil on one eye, and a single winding coil on the other eye to confirm vergence. Head acceleration was measured by a bite bar accelerometer. Immediately before surge onset in darkness, subjects viewed a luminous target 25 or 50 cm from the interocular midpoint, and displaced 10 degrees to the right or left. The target was extinguished 30 to 60 ms before randomly varied onset of 10 surges for each condition. Surge direction was randomized for the 50 cm target, but was always aft for 25 cm to avoid collision. LVOR velocity gain was determined 100 to 200 ms following surge onset as percentage of geometric ideal.

In all subjects, the centered target was associated with a vergence LVOR. Forward surge evoked a convergence slow phase, and aft evoked divergence. Absolute vergence magnitude was greater, but gain less, for the 25 than 50 cm target. For eccentric targets, timing and gain were similar in the two eyes but LVOR magnitude was strikingly greater for the contralateral than ipsilateral eye. This was geometrically appropriate, since the ipsilateral eye was nearly aligned to the target, and the contralateral eye was far eccentric. For the 50 cm distance and aft motion, ipsilateral eye slow phase gain in normal subjects was 0. 53±0. 08, while contralateral eye gain was 0. 58±0. 04; in UVD subjects, ipsilateral eye slow phase gain was 0. 47±0. 09, while contralateral eye gain was 0. 52±0. 07. At 25 cm, ipsilateral eye slow phase gain in normal subjects was 0. 62±0. 10, while contralateral eye gain was 0. 57±0. 04; in UVD subjects, ipsilateral eye slow phase gain was 0. 46±0. 05, while contralateral eye gain was 0. 49±0. 09. Latency of this horizontal LVOR was 53±4 ms in normal subjects, but significantly prolonged to 96±5 ms in UVD ($P<0.0001$). In addition to the slow phase LVOR, subjects often made compensatory saccades with latencies as short as 50 ms. In both subject groups, control experiments showed gain to be higher under comparable conditions when the target remained visible than when extinguished.

Normal and UVD subjects exhibit a short latency, disconjugate slow phase horizontal surge LVOR that depends on horizontal target location, often augmented by saccades. Gain was similar and symmetrical, but latency almost doubled in the UVD group, whose greater age might have contributed to the prolongation.

**BP11.2**

**The Mechanism of Homing Pigeons - The lagena is a key element to geomagnetic sensory system for birds**

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The lagena is often referred to as the third otolithic organ, and is believed to be a sensory organ for the three dimensional sense. It is notable that the lagena is found in vertebrates ranging from cartilaginous fishes to birds, but is not present in mammals.

The recent finding of magnetic materials in the lagenal otoliths of fish and birds raises the possibility that these structures might be key elements in the elusive magnetic sensory system.

Behavioral experiements of the homing abilities of pigeons after sectioning their lagenal nerves or interfering with the function to their lagena with magnets (0. 5-5 Gauss) were done, using 30 control birds and 21 treated birds from the same loft of racing pigeons. The result of homing test of both the controls and the treated pigeons clearly indicates the magnetic influence over and the lagenal function in pigeon's navigation ability. The treated pigeons were either lost or significantly delayed in their coming back, while the controls returned within 30 minutes after the release. Thus the birds' lagena is a unique organ, and it may be concluded that the lagena is a key element to magnetic sensory system for birds.

**BP11.3**

**Conjugate Vertical Eye Movements During NO Linear Translation Compensate for Translation and Tilt**

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Linear acceleration, which stimulates the otolith organs, generates compensatory eye movements for linear translation (translational LVOR) and for tilt relative to gravity (tilt LVOR). Previous investigators have studied these LVORs separately. The two LVORs, however, should work together during linear translation, because inertia and gravity form tilt stimuli. To understand the interaction between the two LVORs, we focused on conjugate vertical eye movements during naso-occipital (NO) linear translation, because these eye movements compensate for both translation and tilt. Geometric considerations revealed that in order to maintain perfect compensations, translational LVOR depends almost linearly on vertical gaze eccentricity, while tilt LVOR does not. Therefore, the two LVORs could be identified by their response properties at different vertical gaze eccentricities.

In this study, we used alert Japanese monkeys (Macaca fuscata), which had been trained to fixate small target spots. The monkey was seated in a chair mounted on a linear sled (Nippon Thompson Co. , Ltd) with its head secured in darkness. The sled riding on linear bearings and driven by a lead screw connected to an AC servomotor oscillated sinusoidally (0. 5 - 4 Hz, 0. 1 - 0. 45 g peak) along the NO axis. One of the three LED target spots (3 cm above, 0 cm, 3 cm below from the eye level) appeared on a screen 35 cm away from the monkey for 500 ms. When the spot was extinguished, the sled started to move. Horizontal and vertical eye positions were recorded binocularly at 1 kHz using an electromagnetic search-coil system (Enzanshi-Kogyo). The vertical eye response sensitivities (amplitude of eye rotation / amplitude of sled translation,

deg/cm) were plotted against vertical gaze eccentricities (deg). Slopes and intercepts were calculated using linear regressions (R > 0. 85) for the data.

The gain in translational LVOR (slope of actual response / slope of ideal response) was almost 1 at 4 Hz, which indicates nearly perfect compensation. It decreased as the frequency decreased and was around 0. 7 at 0. 5 Hz. The gain in tilt LVOR (intercept of actual response / intercept of ideal response) was about 0. 2 at 0. 5 Hz. It decreased as the frequency increased and was less than 0. 001 at 4 Hz. These results support the frequency-dependent parsing of otolith input into a high-pass translational LVOR and a low-pass tilt LVOR in conjugate vertical eye movements during NO linear translation. (This study is supported by the Japan Space Forum. )

**BP11.4**

**Expectation and short-term learning in the interaural translational (t)-VOR**

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We recorded the oculomotor responses (magnetic search coils) to abrupt high-acceleration interaural head translation in 4 normal subjects viewing an earth-fixed (EF) or head-fixed (HF) target at 15 cm distance, in otherwise complete darkness. There were 5 paradigms: random interleaving of EF and HF targets with random direction of head movement (RND), known target behavior with random head movement direction (EF-R or HF-R), known target behavior with predictable (P) head movement direction (EF-P or HF-P). For all conditions we determined a 'gain' with respect to ideal for the EF target, using the ratio of the recorded/ideal eye velocity over a 20 msec epoch around the time of peak head velocity (usually occurring about 100 ms after onset of head motion).

We found no significant differences in gain between HF and EF trials in the RND condition, with an average gain of about 30% of the ideal. Average traces of responses in the EFR and HFR conditions differed as early as 20 ms after the onset of head motion. The average gain was higher (P<0. 01) for each subject in EFR than in HFR (overall averages, 0. 33 vs. 0. 28). Average traces of responses to EFP and HFP conditions differed from the onset of head motion, the average HFP trace showing an initial anti-compensatory eye movement (same direction as the head) that often began even before the head. The average gain was higher (P<0. 01) for each subject in EFP than in HFP (overall averages, 0. 39 vs. 0. 20). To HFP responses there were occasional saccades in the direction opposite to head motion (taking the eye away from the target) in all subjects implying they were 'preprogrammed' for the normal EF condition. Finally, a progressive decrease of gain was observed in HFP responses over the course of the individual set of trials.

Our findings emphasize the importance of cognitive factors including 'effort of spatial localization' and knowledge of the direction of head motion in modifying the response of the t-VOR. Preprogramming of saccades to maintain foveal fixation during head translation is also an important component of the normal t-VOR.

**BP11.5**

**VOR Responses to Step Caloric Stimulation Reveal Asymmetries Caused by Canal-Otolith Interactions**

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It has long been known that horizontal VOR responses to caloric stimulation are larger with the subject in a supine position than in the prone position. This supine/prone asymmetry has generally been attributed to a direct thermal effect on afferent nerve activity in addition to the predominant convection effect due to changes in endolymph density. We used long duration caloric stimulation with rapid changes in head/body position into supine and prone orientations (i. e. "step caloric" stimulation) to investigate this phenomenon.

Twelve subjects participated although complete data were only obtained on 6 subjects due to motion sickness. The caloric stimulus was applied binaurally using modified clinical closed loop irrigators to deliver either right cold (33 deg C)/left warm (41 deg C) or right warm/left cold irrigations. Subjects were initially positioned 20 deg nose down from Reid's plane to place the horizontal canals near the horizontal plane. The caloric stimulus was applied for 2 minutes in this position to establish a stable thermal gradient in the inner ear. The irrigation continued for an additional 7. 5 minutes while the subject was sequentially orientated 90 deg nose up (NU) from the initial orientation, back to the initial orientation, and 90 deg nose down (ND) from the initial orientation. These orientation changes were repeated 3 times with each orientation held for 30 s. An additional control trial lasting 7. 5 minutes was also performed with the subject in the 20 deg ND ("null") position. The peak slow phase eye velocities were measured at the end of the control trial in the 20 deg ND orientation.

Results showed the expected prone/supine response asymmetry with mean eye velocity magnitudes of 50. 6 deg/s in the supine position and 32. 7 deg/s in the prone. Only small responses of about 2 deg/s were recorded in the 20 deg ND orientations with the response direction consistent with the predicted direct thermal effect. These control stimulation results indicate that the direct thermal effect makes only a small contribution that does not account for the large supine/prone asymmetry observed.

We postulate that the observed supine/prone asymmetry is primarily attributable to the central nervous system's interpretation of the "conflicting" motion cues received from semicircular canals and otoliths. Specifically, this sensory conflict is resolved by central neural processing that uses canal and otolith motion information to estimate head rotation, gravity orientation, and linear acceleration of the head. The yaw rotational cues evoked by caloric stimulation elicit both an angular VOR and an illusory yaw tilt, as was informally reported by some subjects, indicating that the internal estimate of gravity orientation has been altered. The combination of an altered estimate of gravity orientation and an unchanging signal from the otolith organs produces an internal estimate of linear acceleration, eliciting a translational VOR response. For caloric stimulation, the magnitude of these angular and linear VOR components always add in the supine position, and subtract in the prone position,

accounting for most of the observed supine/prone response asymmetry. (Supported by NIH/NIDCD grant DC04158)

**BP11.6**

**Click-Evoked Potentials on the Neck of the Guinea Pig**

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The click-evoked vestibulo-collic reflex, so-called vestibular evoked myogenic potential (VEMP) has been used as a new clinical test of the vestibular system. However, an animal model of this test has not been established. For the basic research of this test, the development of an animal model is essential. In order to establish an animal model of the VEMP, we recorded click-evoked potentials on the neck of the guinea pig, of which primary vestibular afferents respond to clicks.

Materials and Methods. Healthy guinea pigs were used for this study. In addition to the normal control group, we used amikacin-administrated guinea pigs and gentamicin-administrated guinea pigs. Amikacin-administrated guinea pigs (AA group) were intramuscularly given amikacin (450 mg/kg body weight/ day x 12 days). Gentamicin-administrated guinea pigs (GA group) were intramuscularly given gentamicin (90 mg/kg body weight/ day x 20 days). All the guinea pigs used in this study underwent caloric tests with ice water prior to the recording of evoked potentials. Under the general anesthesia by intraperitoneal injection of pentobarbital sodium (imp. , 45 mg/kg body weight), the auditory brainstem response (ABR) was recorded. Following the recording of ABR, evoked potentials in the neck by clicks were recorded using silver-ball electrodes. To place electrodes, the pre-vertebral muscles were exposed by the ventral approach. Electrodes were placed on the longs colli muscle at the C3 level and in the muscle on the sternum. Clicks (0. 1msec, 105dBSPL) were presented to the ear through the specula connected with a headphone at a rate of 5Hz. Two-hundred responses were band-pass filtered and averaged.

Results. Caloric responses were absent only in guinea pigs of the GA group. Thresholds of the ABR were highly elevated only in AA group. In the control group, a distinctive negative peak (NP), of which the latency was 6. 8msec on the average, was observed when clicks (0. 1msec, 105dBSPL) were presented. The thresholds of NP were 90-100dB above those of ABR. NP was also recorded in AA group while NP was not observed in GA group. After the section of the 8th cranial nerve, NP was abolished.

Discussion. NP was recorded on the neck muscle. The threshold of NP was as high as that of VEMP in humans. We considered that NP could reflect the vestibulo-spinal tract that is supposed to be the pathway of the VEMP in humans. NP was not affected with the selective cochlear destruction by amikacin while NP was abolished with the selective vestibular destruction by gentamicin. These results suggested that NP is not likely to be of cochlear origin but rather of vestibular origin.

Conclusion. NP in this study is expected to be a good experimental animal model of the vestibulo-collic reflex by clicks.

**BP11.7**

**Unilateral otolith function testing - Is the utricular function additive ?**

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The utricle plays a crucial role in the detection of gravity. Knowledge about its function is usually obtained using lateroflexion tests or centrifuge tests. The newly developed unilateral otolith function test, based on work by Von Baumgarten in the early 90ies, and further elaborated by A. Clarke in Berlin is a method to evaluate each utricular system separately.

Material and methods. We present a modified paradigm of this test during which the subject is rotated about an earth vertical axis at a velocity of 400 degrees per second and consecutively translated (2 mm/s) along an interaural axis for 4 cm to the right and to the left. In each eccentric position along this path, both utricles are centrifuged at a different magnitude. When the axis of rotation is positioned through one utricular system, only the contralateral utricle is stimulated. Consequently, the centrifuged utricle feels an outward pulling force equal to 0. 4g, corresponding to a gravito-inertial acceleration (GIA) tilt of 21 degrees. This utricular stimulation induces an ocular counter rolling (OCR), that is measured on-line using three dimensional video-oculography, a method validated by a special calibration device.

Model for utricular function. We present a theoretical model and experimental data describing a linear relationship between the OCR and the GIA tilt, felt by a transducer placed at the centre of the head behind the subject: (OCR = intercept + slope x GIA tilt). The function of right and left utricle is assumed to be additive during the unilateral otolith function test, as long as the axis of rotation is situated between both utricular systems. The slope of the linear regression is a measure of the responsiveness of both utricles (similar to the gain obtained from rotary chair testing with electronystagmography), whereas the intercept is a measure of lateralisation of the utricular response (similar to labyrinth asymmetry obtained in caloric testing).

Results. Healthy subjects (N=34) In a group of 34 healthy subjects, this linear relationship (OCR as a function of tilt) was measured for both eyes. The average (± se) responsiveness yields -0. 222 (± 0. 010) deg_OCR/deg_tilt and the lateralisation = -0. 49 (± 0. 19) deg_OCR.

Acoustic Neuroma subjects (N=14). The responsiveness of the utricular system in patients with acoustic neuroma (UVD), after surgery, is only half of the value in healthy subjects. Therefore, according to the additive model should the slope of the OCR tilt relationship only be half of the slope in healthy subjects. Data obtained from 14 UVD patients yield 0. 107 (± 0. 007) deg_OCR/deg_tilt, as predicted. The intercept for right UVD patients is 0. 73 (± 0. 22) deg_OCR, where the intercept for left UVD patients is 0. 22 (± 0. 23) deg_OCR, as predicted by the theoretical model.

Conclusion. The data are well in accordance with the theoretical model proposing an additive function of the utricle. This model and the data provide a quantitative tool for evaluating utricular function in subjects, especially when no proper knowledge of the vestibular diagnosis is available

**BP11.8**

**Dependence of the Gain of the Human Vertical Angular Vestibulo-Ocular Reflex on Gravity**

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The gain of the vertical angular vestibulo-ocular reflex ($aVOR_v$) was adaptively decreased in five subjects by sinusoidal oscillation for one hour at 0. 2 Hz in a subject-stationary visual surround in the left side down (LSD) position. Gains were tested by sinusoidal oscillation about a spatial vertical axis while subjects were tilted in 15° increments in the roll plane from the LSD to the right side down (RSD) position. The $aVOR_v$ gain changes were maximal in the position in which the gain had been adapted, and declined progressively as subjects were moved from this position. Gain changes were plotted as a function of head orientation and fit with a cosine function. The amplitude of the sinusoid, i. e. , the *gravity-dependent gain* change, was 15. 0±9. 2% with a phase of –126±16° with regard to the upright (0°). There was also a shift in the bias level of the fitted cosines, i. e. , *gravity-independent gain* change, that was –29. 0±10. 0%. The induced gain changes were long lasting and declined to zero gradually over a three-day period.

The possible clinical significance of the dependence of gain change on the position of adaptation is still unknown, as are the symptoms that can evolve from pathology of those regions responsible for the gain changes. An obvious clinical syndrome that might be associated with the prolongation of adaptive changes is "mal de debarquement", in which adaptation to specific motions can be held for long periods of time after leaving vehicles, ships or airplanes. Thus, we have demonstrated that adaptation of the aVOR in humans is oriented to gravity and that this orientation is stored for substantial periods.

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**BP11.9**

**Eye Movements in the Tullio phenomenon**

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Patients with the Tullio phenomenon have been reported to show various different eye movements such as tonic torsion (Dieterich et al. 1989) and nystagmus (Ostrowski et al. 2001). Recently it has been reported that in some patients at least, the rotation axis of the nystagmus is collinear with an axis orthogonal to the anterior (i. e. superior) semicircular canal on the stimulated side. Most of these patients have a bony dehiscence of the superior semicircular canal into the middle cranial fossa (Minor et al. 1998). It appears that sound somehow deflects the crista of the superior semicircular canal in the excitatory (ampullofugal) direction. Most of these patients also have abnormally low threshold and abnormally high amplitude vestibular evoked myogenic potentials. It appears that sound also somehow excites the saccular macula on the affected side (Watson et al. 2000).

We wondered whether sound could also excite the other vestibular organs and in order to answer this question we measured three-dimensional eye movements in patients with Tullio phenomenon to see if the lateral and posterior semicircular canals could also be activated. Patients who complained of vertigo and imbalance in response to sound were stimulated with pure tone ranging from 750, 1000, 1500 and 2000 Hz at 110 dB HL. During the sound stimulation, three-dimensional eye movements of the patients were recorded with dual scleral search coils. The axis of eye rotation was determined using three-dimensional vector analysis of the slow phase component of the nystagmus and was compared with the published on-directions of the stimulated semicircular canals. In some patients, the axis of eye rotation was aligned with the on-direction of the superior semicircular canal showing the superior canal afferents are stimulated. In one patient observation of the time course of the nystagmus showed that the axis of eye rotation evolved from initial alignment with superior canal to that of the lateral canal in the same ear over a period of 10 seconds during the sound stimulation.

This study suggests that sound stimulation in patients with Tullio phenomenon due to superior semicircular canal dehiscence can stimulate other vestibular structures in addition to the superior semicircular canal.

**BP12.1**

**Cortical correlates of vestibulo-ocular reflex modulation: a PET study**

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To elucidate cortical correlates of vestibulo-ocular reflex modulation, we observed cortical activation during fixation suppression and habituation of caloric vestibular nystagmus by positron emission tomography (PET) in 12 normal subjects. Caloric vestibular stimulation activated the middle and posterior insula, inferior parietal lobule, temporal pole, right fusiform gyrus, lingual gyrus, and cerebellar vermis and hemisphere. The activation of the insular region and the inferior parietal lobule was lateralized depending on the direction of the nystagmus. Caloric nystagmus was suppressed with visual fixation, during which the area around the right frontal eye field, temporal pole, inferior temporal gyrus, broad area in visual cortex including fusiform and lingual gyrus, cerebellar uvula/nodulus and flocculus were activated, while vestibular cortices were deactivated. The caloric nystagmus habituated with repetition of stimulation. With habituation, we observed activation in the right anterior cingulate gyrus, left post-central gyrus, and left lingual gyrus, and deactivation in the right insula, bilateral inferior parietal lobules, and bilateral inferior temporal gyri. The regions that showed significant co-activation with fixation suppression and habituation of caloric nystagmus were the left lingual gyrus, right primary visual area and uvula of the cerebellum. Regions that showed significant co-deactivation with habituation and fixation suppression of

caloric nystagmus were the bilateral insula, bilateral inferior parietal lobules/superior temporal gyri, and left cerebellar hemisphere.

The present results support previous observations that parieto-insular cortex and inferior parietal lobule are involved in processing of vestibular information, and, in addition, suggest that the activation may depend on the direction of nystagmus. Deactivation of vestibular cortices during visual fixation supports the concept of inhibitory visual-vestibular interaction in the cortex. Significant activation of the cingulate, post-central and visual cortices accompanying reduction of caloric response with repeated stimuli suggests possible involvement of these regions in vestibular habituation. Common activation of the visual cortex and the cerebellar vermis by both visual suppression and habituation of VOR suggests that these two mechanisms are not completely independent but may share some cortical and sub-cortical regions.

**BP12.2**

**Rollvection vs. Linearvection: Comparison of Brain Activations in PET**

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Objective: To investigate the differential activations and deactivations during large-field visual motion that induces the sensation of apparent linear or circular (roll) motion.

Background: In an earlier PET study using visual motion stimulation that induced vection in roll we found bilateral activations of a medial parieto-occipital brain area and simultaneous deactivations of the posterior insula and retroinsular regions (the parieto-insular vestibular cortex - PIVC) [Brandt et al. Brain 1998;121:1749-58].

Design/Methods: Eleven healthy male volunteers (right-handed, 29 to 60 years of age) were examined in a Siemens/ECAT EXACT HR+ PET scanner (total axial field of view of 15. 28 cm; 63 slices) using O-15 water-PET. For visual stimulation subjects wore a helmet in which a display was mounted with the field of view subtending 100 deg in horizontal and 60 deg in vertical dimensions. Three conditions were presented to the subjects: A) stationary dots (rest); B) dots accelerating in radial directions away from a focus of expansion in the middle of the screen (forward linearvection); C) dots rotating counterclockwise (clockwise rollvection). Prior to random effects statistical group analysis (p =0. 001, uncorrected), data were realigned, spatially normalized, and smoothed using SPM99.

Results: During rollvection (C-A) bilateral activations were seen in the visual cortex including PO (BA 17-19; 5105 voxels; t-value: 11. 13) and in the motion-sensitive area MT/V5 (BA 19/37). Deactivations were found in the middle temporal gyri bilaterally, in the right posterior insula, and in the left anterior cingulate gyrus.
Linearvection (B-A) also induced bilateral activations in the visual cortex including PO (BA 17-19; 9725 voxels; t-value: 15. 34) and MT/V5. Simultaneously rCBF decreases occurred in the cingulate gyri bilaterally, in the right inferior parietal lobule (BA 40), and in the right posterior insula.

Statistical comparison of the conditions linearvection minus rollvection showed bilateral activations in the lower visual cortex (BA 17/18; 2556 voxels; t-value: 10. 03).
In the comparison rollvection minus linearvection the largest cluster was seen in the superior parietal gyrus (BA 7; 38 voxels, t-value: 7. 52), smaller clusters were found in the precuneus (BA 7); there were no activations in the occipital gyri.

Conclusions: Linearvection and rollvection during large-field visual motion stimulation led to activations of neighbouring, partially overlapping visual areas including PO (BA 17-19). These activations were larger and more significant during linearvection. Thus, with the paradigm used, the mediation of rollvection and linearvection is represented in partially overlapping visual cortical areas. Both stimuli led to simultaneous deactivations of the posterior insula as described earlier for roll motion, indicating an inhibitory interaction between the visual and the vestibular system.

**BP12.3**

**Measurements of cortical magnetic responses to visually-induced apparent self-motion perception**

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Electrophysiological studies in monkeys identified regions of the cerebral cortex that receive vestibular inputs including the poserior part of the insula (parieto-insular vestibular cortex: PIVC), portions of the intraparietal sulcus (area 2v), and the central sulcus (area 3aV). However, the detection of self-motion during constant velocity movements depend entirely on visually-induced apparent self-motion perception, or vection, because the vestibular system can sense only accelerations. In this study, the cortical sites that process sensations of apparent self-motion perception were studied using neuromagnetic measurements.

Visual motion stimuli were projected onto a tangent screen and the test field subtended 110 degrees by 74 degrees. Three conditions were presented to the subjects. Condition I consisted of a black background and a total of 100 white dots, randomly distributed in the field of view and moving in random order. This visual motion stimulation did not induce any apparent self-motion (no-V). In condition II, all dots rotated counter-clockwise at a constant angular velocity of 40 degrees/s. This condition induced an apparent self-motion of clockwise-rotation in the roll plane (CV). Condition III was an optical flow stimulus, which induced a linear apparent self-motion backward (LV). Dots appeared at the edges of the screen and traveled linearly to the center of the screen.

Seven healthy volunteers (5 males, 22-41 years, right-handed, normal or corrected-to-normal vision), who reported experiences of self-motion perception during measurements, took part in this study. Subjects were requested to fixate binocularly on a central point on the screen at a distance of 60 cm during each motion

stimulation task. Measurements of magnetic fields were carried out using a 122ch whole-head neuromagnetometer (Neuromag-122TM, 4-D Neuroimaging Ltd. , Helsinki, Finland) in a magnetically shielded room. Frequency analyses were applied to the magnetic data to look for modulation of the oscillatory activities.

Oscillatory activities within the frequency range of 6-14 Hz, in which alpha, myu, and tau activities are included, were significantly smaller in conditions II and III than that in condition I in the temporal and parietal regions. On the other hand, larger activities in the frequency range 0. 03-3 Hz were observed in conditions II and III compared to condition I. These synchronizations and desynchronizations may reflect activities of the PIVC and the area around the intra-parietal sulcus. These results suggest that the vestibular cortices are activated by sensations of apparent self-motion and integrate multi-modal information.

**BP12.4**

**Visual and vestibular cues in judging the direction of 'up'**

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Astronauts in microgravity frequently experience reorientation illusions in which they or their world appear to flip and 'up' becomes arbitrarily redefined. The perception of 'up' is the result of a combination of visual and non-visual cues. Non-visual include the sense of body ("idiotropic vector") and the direction of gravity ("gravotropic vector"). Visual cues include the polarized environment as well as the polarity of individual objects and the sight of one's own and other people's bodies. On earth we are exploring the importance of visual cues that might affect the perceived direction of up. Understanding factors that affect the perception of up will enhance our understanding of perception in microgravity and may lead to countermeasures for reorientation illusions.

In the absence of information about the origin of illumination (such as being able to see a table lamp) people interpret surface structure by assuming that the direction of illumination is from above. Here we exploit this phenomenon to explore the influence of the frames of reference defined by head and body orientation, gravity and visual cues on judgments of 'up'.

Two sets of four grey, shaded discs were used that differed orthogonally in the polarity of their shading. One set of disks were shaded light-top, light-bottom, light-left and light-right. The second set was shaded in 30 deg steps in a 90 deg quadrant between light-top and light-left. Observers indicated with a four-button response pad which of the four discs appeared most convex and thus indicated the direction of their perceived above. 192 sets of discs were shown in a cross formation on a grey laptop screen arranged with the keyboard in the normal configuration relative to the body. Observers were positioned (i) lying on their right side in an upright room, (ii) sitting upright in an upright room, (iii) lying prone with head inverted in an upright room, or (iv) lying on their right side in a specially constructed room tilted by 90 degrees.

The pattern of responses indicates that the perceived direction of 'above' is influenced by both the direction of gravity and the visual frame (defined by both the display and the surrounding room). When the room was tilted, the visual cue pulled the perceived direction of 'above' away from the direction defined by gravity. This suggests that the interpretation of "up" can be influenced by particular visual cues.

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**BP12.5**

**Effect of Vestibular Galvanic Stimulation (VGS) on subjective vertical and perception of body segments**

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Information provided by the vestibular system has been extensively studied for its fundamental role in the neural coding of space perception. One recurrent problem with some methods classically used to stimulate the vestibular system, like head tilt, body tilt or alteration of the gravito-inertial field, resides in the fact that they generate concurrent proprioceptive and somatosensory signals. Galvanic vestibular stimulation (GVS) has the particular advantage of selectively activating the vestibular system. This technique consists of applying moderate direct current between the mastoid processes, which modulates the spontaneous firing of vestibular nerve fibers: increased frequency on the cathode side and decreased frequency on the anode side. Effects of GVS have been demonstrated on various sensorimotor functions, such as the control of eye movement , posture, and walking. Our study deals with the effects of galvanic vestibular stimulation on the perception of spatial orientation. This stimulation technique could be used to induce sensations of body motion,for instance in vehicle simulators or in virtual reality systems.

This study investigated whether the tilt of the subjective vertical induced by GVS, demonstrated by asking subjects to set a rod to the vertical, was specific to the visual modality or could be found in two tasks relying on proprioceptive and somatosensory cues. In all cases, settings were significantly deviated in the direction of the anode, but errors were smaller in the proprioceptive tasks than in the visual task.

We propose that the effects observed in the proprioceptive modality reflect only a modification of the central representation of gravity, whereas visual effects are also in part the consequence of unregistered ocular torsion. Besides, stimulating the vestibular apparatus gives rise to clearly dissociated effects on the subjective vertical, on the one hand, and the perception of body orientation, on the other hand. The results are compared with the current models of spatial orientation.

**BP12.6**

**Changes in ocular torsional position produced by a single moving visual line - visual "entrainment"**

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It is well established that a large visual stimulus slowly rotating in torsion around a naso-occipital axis causes both eyes to tort. Many of the factors controlling

this optokinetic torsion have been identified (field size, angular velocity, spatial frequency etc). In the course of recent studies we used our 3-d video system (VidEyeO) to measure ocular torsion simultaneously with visual perceptual judgements whilst the subject moved a simple visual line in an otherwise darkened room to the subjective visual horizontal (SVH) or subjective visual vertical (SVV) using the standard method of adjustment paradigm; the test line appeared at a roll-tilt angle offset from the SVV or SVH target position by + or - 20 degrees and started moving toward the target at constant velocity of 5degrees/sec.

We found that such a minimal visual stimulus, a single short moving visual line, can induce changes in ocular torsional position of up to 3 degrees. While the visual line was moving the torsional position of the eye changed such that the visual line "dragged" or "entrained" the eye to rotate in torsion. When the line stopped, the eye rolled back towards the resting torsion position it had before the movement started. This result is of interest since moving lines to the SVV or SVH using the method of adjustment is a widely used method for measuring visual perception and so this entrainment may possibly have an influence on judgements of visual stimuli in this situation.

We show that entrainment of torsion by the moving visual line is a reliable and repeatable effect however there are 1) considerable individual differences between subjects 2) some subjects show consistent asymmetries in torsional entrainment for CW and CCW rotations and 3) there are consistent differences in lines moving to the SVV as opposed to the SVH : with most subjects showing larger and more consistent torsional entrainment for lines moving to the horizontal than lines moving to the vertical. In all of the studies the subjects were instructed to maintain fixation on the central dot of the line (which was composed of 11 LEDs) so that torsion produced by changes in eye position was not a factor in this situation.

**BP12.7**

**Using Post-Illusory Tilt Rotations to Study How the CNS Estimates Gravity and Linear Acceleration**

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We used a new paradigm referred to as "post-illusory tilt rotation" that includes 3 phases (A, B & C discussed below). (A) An upright subject is accelerated to a 350deg/s on-center yaw rotation. (B) After 40s, when signals from the semicircular canals have decayed to near-zero, the subject is translated (5s) along the centrifuge arm to a 0. 22m radius. The otoliths then measure a GIF tilted 40deg with respect to earth-vertical. The subject is initially oriented with respect to the centrifuge arm so that the radial movement is either inter-aural (Facing-Motion [FM] and Back-to-Motion [BM] with N =7), naso-occipital (Facing-Center [FC] and Back-to-Center [BC] with N=8) or along the 2 other axes that are 45deg from either the inter-aural or naso-occipital axis ([FC-FM, FC-BM, BC-FM, BC-FM] with N=6). C) After 35s, the subject is simultaneously translated to a 0. 43m radius and decelerated to a 250deg/s yaw rotation (both in 5s). Before and after (C), the GIF is identical. During (C), subjects experience a "post-illusory tilt rotation" since canals measure a 100deg/s yaw rotation, while otoliths measure a quasi-constant GIF (the GIF tilt with respect to earth-vertical varies less than 3deg). Due to canal cues, we hypothesize that the estimate of gravity, originally tilted toward alignment with the GIF, is rotated in yaw away from the GIF. We further hypothesize that the CNS elicits a non-zero estimate of linear acceleration, even in the absence of true linear acceleration. A component of this linear acceleration will align with the inter-aural axis, eliciting a horizontal translational VOR. The inter-aural estimate of linear acceleration and the horizontal translational VOR are predicted to vary sinusoidally with subject orientation.

**BP12.8**

**The Subjective Visual Vertical: The Initial Light Bar Orientation Affects the Outcome**

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The subjective visual vertical (SVV) test is a method to evaluate the perception of the head position relative to gravity. Moreover, the SVV is a sensitive measure of otolith and especially utricular function. The essence of the test consists of the alignment of a dimly illuminated bar to the gravitational vertical in a totally darkened room. In our experiment, the SVV was measured in 38 healthy subjects with the head laterally flexed (between 20º and 50º) to the right and to the left. The initial orientation of the laser beam was alternately set clockwise and counterclockwise with respect to the earth vertical (random between 5º and 20º).

Parallel and anti-parallel paradigms. Various studies reported the E-effect or Müller phenomenon when the head is tilted less than 60ºDD370º. This E-effect consists of a deviation of the SVV beyond the true vertical because of an overestimation of the head tilt angle. This study shows that the initial lightbar orientation affects the outcome of the subjective visual vertical test when the head is laterally flexed. Two paradigms are distinguished according to the initial orientation of the laser beam. First, in the so called 01Cparallel01D paradigm, the initial orientation of the laser line is relatively parallel to the length axis of the tilted head. Second, in the 01Canti-parallel01D paradigm, the initial orientation of the line is relatively perpendicular to the length axis of the tilted head.

Results & conclusions. The present study demonstrates that the E-effect is annihilated if the initial orientation of the light bar is relatively parallel to the length axis of the tilted head: the SVV coincides the true vertical. The E-effect is only observed when the initial orientation of the light bar is not parallel with the length axis of the tilted head. The only difference in both conditions is the light bar initial orientation, since the head orientation is kept constant.

We hypothesise that in the parallel paradigm the brain recognizes that the light bar is more or less aligned with the length axis of the head. It then uses the utricular information to calculate the correction with respect to the real vertical for the proper adjustment. In the anti-parallel paradigm however, the brain cannot align the offered light bar with the length axis of the head and therefore cannot calculate the appropriate correction, based on utricular information, to adjust the light bar.

**BP12.9**

**Vertigo Matching with Vection Stimuli in Chronic Dizziness Patients**

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When asked to describe their symptom, patients with chronic vertigo will often respond with a demonstration of an oscillation side to side at a frequency of approximately 0. 5 Hz. Such a demonstration is curious in the light of the wide range of frequencies and directions that the vestibular apparatus codes for. It might be expected that motion sensations that are chaotic or inconsistent in direction and frequency would be induced by peripheral vestibular disorders.

We wished to investigate the characteristics of vertigo in chronic dizziness patients to determine if we could provide a reasonable simulacrum of their sensation and find out the direction and frequency of these oscillations. We used a vection stimulus presented to subjects with a head mounted display. Methods. 15 patients with vertigo complaints for greater than 6 months were selected for the matching procedure. They wore a head mounted display that presented an image created with a computer graphics system. Subjects indicated the direction of their vertigo sensation, horizontal or vertical, and an oscillating scene was shown to them in the appropriate direction. The oscillation frequency was controlled by the subject and they varied the frequency until it matched their sensation. Two runs were done with a high (>5Hz) and low (<0. 1Hz) initial frequency. 4 subjects were tested on a second day. Subjects were asked to give a 1 to 10 rating of the quality of their vertigo match.

Results. 14 subjects were able to use the vection stimulus as a match for their vertigo. All but one indicated a horizontal (ie. interaural) direction of their motion sensation. The data appears to indicate there are two types of vertigo sensations. In one group, 10 subjects gave ratings of 7 of 10 or greater in quality of reproduction of vertigo by the vection stimulus. This group had an average frequency of 0. 61 Hz +/- 0. 25. Their retest values were within 18% of each other. In 4 subjects tested on a second day, their average match frequency was within 12% of the first. One subject reported 2 frequencies. The low quality match group (<7 of 10) had an average frequency of 1. 66 Hz.

Conclusions. The method of using a vection stimulus as method for vertigo matching appears to be useful. Several subjects remarked how the display allowed them to demonstrate something they could not describe verbally. It appears that a majority of chronic vertigo subjects have a specific vertigo frequency on the order of 0. 5 Hz, usually in the horizontal direction. The specificity of the sensation suggests that efforts for adaptation of this sensation might be directed at that frequency.

**BP12.10**

**Relationship of Vertigo and Nystagmus during Caloric Testing**

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Traditional clinical teaching states that in central vestibular disease nystagmus bears only a weak relationship to the intensity of vertigo felt by the patient. In our clinic it is a common clinical finding that the intensity of the peripheral nystagmus induced by the manoeuvres to provoke benign positional vertigo also has only a weak relationship to the intensity of the subjective feeling of vertigo. To explore the relationship between the intensities of vertigo and nystagmus in peripheral vestibular stimulation data were collected during caloric testing.

123 consecutive patients in whom a caloric test was performed were asked to indicate the intensity of their vertigo after each irrigation on a 5 point scale ranging from 0 (no vertigo) to 4 (strong vertigo with nausea). All patients were asked if the vertigo felt was spinning or non spinning and 80 patients were also asked to indicate the direction of spinning in case this sensation occurred. The maximal slow phase velocity (SPV) reached after each irrigation was recorded.

The data of the 30°C left irrigation are presented here. This stimulation induces a right beating nystagmus and in theory a feeling of spinning to the right. Of the 123 patients 43(35%) patients felt no vertigo, 72 (58.5%) had spinning vertigo and 8 (6.5%) had non-spinning vertigo. There was a significant correlation between maximal slow phase velocity and vertigo score but the correlation coefficient was low r=0.44.

In the subgroup of 80 patients asked to indicate the direction of the spinning n= 27 (33.8%) felt no vertigo, in 7 (8.8%) the vertigo had a non spinning character, in 11(13.8%) it was spinning but they could not tell the direction, 10 (12.5%) felt it was left spinning and only in 26 (32.5%) it was right spinning.

The relationship between subjective vertigo and lateral nystagmus induced by a caloric stimulation is very variable. The SPV of the nystagmus has little predictive value as to the intensity, the spinning/non spinning character of the vertigo and even to the direction of the spinning sensation in case it is felt. The findings in this artificially induced nystagmus and vertigo are compatible with the clinical observations in disease related nystagmus/vertigo.

**BP12.11**

**Influence of visual rotational cues on human orientation and eye movements**

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Sensory systems often provide ambiguous information. For example, otolith organs measure gravito-inertial force (GIF), the sum of gravitational force and inertial force due to linear acceleration. However, according to Einstein's equivalence principle, gravitational force is indistinguishable from inertial force. Therefore, the central nervous system (CNS) must use other sensory cues to distinguish tilt from translation. For example, the CNS can use visual cues providing motion information. The GIF resolution hypothesis states that the CNS estimates gravity and linear acceleration such that the difference between these estimates match the measured GIF. Due to sensory interactions, the hypothesis predicts that inaccurate estimates of gravity and linear acceleration can occur. Specifically, the hypothesis predicts that illusory tilt caused by roll optokinetic cues should lead to a horizontal VOR.

To investigate this prediction, we measured eye movements (binocularly using infrared video methods) in

19 subjects during and after roll optokinetic stimulation about the subject's naso-occipital axis (60deg/s, clockwise or counterclockwise). The optokinetic stimulation was applied for 60s followed by 30s in darkness. We simultaneously measured subjective roll tilt using a somatosensory bar. Each subject was tested in 3 different orientations: upright, pitched forward 10deg, pitched backward 10deg. Eight subjects reported subjective roll tilts (>10deg) in directions consistent with the direction of the optokinetic stimulation. Besides the torsional optokinetic afternystagmus, we observed for all orientations a horizontal afternystagmus to the right following clockwise stimulation and to the left following counterclockwise stimulation. These observations are in agreement with the GIF resolution hypothesis that suggests that a subjective tilt in the absence of real tilt should induce a non-zero estimate of inter-aural linear acceleration, and therefore a horizontal VOR. On the contrary, an axis-shift component toward alignment with gravity does not account for these observations since it would reverse between pitched forward and backward orientations. Supported by NIDCD grant DC04158.